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A Journal of Neurology

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PART 1, VOL. 58.

STUDIES IN THE NEUROLOGICAL MECHANISM OF PARATHYROID TETANY.

BY RANYARD WEST,

Beit Memorial Research Fellow.

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INTRODUCTION.

THE paper which follows is a contribution in a certain limited field in the wide problem of the mechanism by which the muscular spasms of tetany are produced.

In recent years the study and the literature of tetany have been considerable. As a condition it is not easy to define, of its essential nature we are ignorant. Its predominant manifestation is of muscular contractions of widespread regional distribution and of divergent forms. In man and in certain higher mammals distinctive postures occur. A variety of changes in the chemical composition of the blood are associated with tetany; the condition has been nevertheless recorded in the absence of such changes. Tetany has been found associated with a number of diseases of the central nervous system, though it also occurs in the absence of any demonstrable disease of the brain, spinal cord or peripheral nerves.

It is profitable to study the mechanism of the production of muscle contractions in a specific form of tetany, that arising from parathyroid

extirpation. Only the neuro-muscular mechanism involved is considered, and this only in certain of its aspects. Similar studies have been made before [1, 2, 3, 4] but the views of the problem as a whole differ somewhat from the one taken here, and not in all cases have my observations and deductions coincided with those of previous writers. Certain phenomena are newly recorded.

Part I.

The Modification of Parathyroid Tetany by Peripheral Nerve Section.

Partial or complete denervation of one hind limb was undertaken in seven dogs. In four, the sciatic nerve was divided in the gluteal region; in the remaining three the combined anterior and posterior roots of segments 3, 4, 5, 6, 7, 8 in the lumbar region of the spinal cord were cut. The operation was done on the left side, extra-thecally, and the cauda equina was transected immediately below the last severed root. Tetany was induced by parathyroidectomy. Eleven observations were made at intervals varying from four and a half hours to twenty days after nerve section.

Parathyroid tetany in dogs may be classified in its motor manifestations as :—

(1) *Tonic tetany*, where continued contraction of a muscle or a group of muscles produces a strongly marked posture.

(2) *Clonic tetany*, where whole muscles, or a large proportion of the fibres of a muscle, contract synchronously or nearly synchronously, producing a violent jerked movement of the limb, or a sharp twitch of an individual muscle. The clonic contractions of tetany frequently occur in a flaccid limb ; they are variable and irregular in frequency, but may reach a rate and occasion grouping suggesting the beating of a kettle-drum. The latter form occurs characteristically in the scalp.

(3) *Fibrillary tetany*, consisting of a rapid repeated contraction of a small group of fibres in one or more areas, not infrequently scattered widely throughout the musculature of the body.

It has been stated by Paton, Findlay and Watson [1] that section of the nerves to any part entirely and immediately abolishes all spasms, tremors and jerkings of the muscles supplied. My observations suggest that, in the case of the dog, if twenty-four hours are allowed to elapse between the nerve section and the onset of tetany, the latter will seldom be seen in the denervated muscles (*see* Table I), but fibrillary tetany can undoubtedly occur in the first few hours after denervation,

and in early stages grouped contractions large enough to be classed as "clonic" have been seen. The tonic (postural) element has, however, not been present in this series. In all cases where comparison was possible, the activity of the tetany was less in the denervated muscles than in the normal opposite limb.

Clonic tetany was clearly seen in the case of tetany precipitated four and a quarter hours after nerve section, and in no other case. (Table I, Dog 1.) In the one case marked "Doubtful Result" (Dog 7, third day), tetany was probably absent, but it was not certain that the limb was flaccid throughout. In all the remaining cases fibrillary tetany was either continuously present or never observed.

Table I shows the time after denervation at which tetany was induced, the presence or absence of tetany in the denervated muscles, and the condition of the opposite hind limb.

TABLE I.

Dog	Site of section	Time after section	Tetany and denervated muscles	Tetany in opposite hind limbs
1.	Sciatic	4½ hours	Chronic and fibrillary tetany in flexors and extensors below knee	Tonic extension, clonic and fibrillary
2.	Spinal roots	{5 hours / 6 hours}	Fibrillary tetany throughout	Fibrillary and slight tonic
3.	Spinal roots	7 hours	Fibrillary tetany in hamstrings, gastrocnemius	Some tonic extensor. Fibrillary active
4.	Sciatic	12 hours	No tetany	(Both sides denervated)
5.	Sciatic	24 hours	Fibrillary tetany in hamstrings	(No observations)
6.	Spinal roots	2 days	No tetany	Tonic, fibrillary, occasional clonic
7.	Sciatic	3 days	Doubtful result	(Both sides denervated)
8.	Spinal roots	3 days	No tetany	Some tonic extensor. Fibrillary active
6.	Spinal roots	4 days	No tetany	Fibrillary
6.	Spinal roots	5 days	No tetany	Tonic, clonic and fibrillary
4.	Sciatic	13 days	No tetany	Tonic and clonic
7.	Sciatic	20 days	No tetany	(Both sides denervated)

Electrical reactions in denervated tetany preparations.—Electrical reactions obtained by a stimulating electrode placed on the skin [7] have been recorded in tetany in dogs [8]. In denervate preparations, apart from tetany, certain anomalous electrical reactions were obtained and are recorded elsewhere [9]. Briefly, a phase of hyperexcitability occurs on about the fifth day after denervation and persists as long as

it has been studied (to the twentieth day). This effect, on the eighth day, is shown in Table II. Table III shows the reactions in the same dog in tetany. It will be seen that while the notable fall of threshold, especially and characteristically, of the kathodal opening current (K.O.C.), has occurred on the normal side, the denervated side has not fallen further. The reading in tetany on the denervated side was higher in each item than it had been since the fifth day of denervation. In this case tetany was precipitated on the twenty-second day. No tetany occurred in the denervated limb.

TABLE II. (BEFORE PARATHYROIDECTOMY.)

Stimulus	Left (denervated, 8th day)	Right (intact limb)
K.C.C.	0·1 milliampere	1·3 ma.
K.O.C.	0·25 ,,	6·0 ,,
A.C.C.	0·15 ,,	2·3 ,,
A.O.C.	0·25 ,,	3·5 ,,

TABLE III. (IN TETANY—22ND DAY.)

	Denervated		
Stimulus	Occasion 1	Occasion 2	Intact limb
K.C.C.	0·5 ma.	0·7 ma.	0·4 ma.
K.O.C.	0·45 ,,	0·2 ,,	0·4 ,,
A.C.C.	0·6 ,,	0·18 ,,	0·8 ,,
	1·0 ,,	0·5 ,,	0·5 ,,

If, however, tetany be induced on the second day after section, and thus before the electrical effects of denervation are apparent, the characteristic fall in threshold occurs. (Table IV.)

TABLE IV. (2ND DAY.)

	Limits of five previous readings	In tetany
K.C.C.	0·5 to 0.8 ma.	0·5 ma.
K.O.C.	5·0 to 10·0 ,,	0·5 ,,
A.C.C.	1·6 to 2·3 ,,	0·2 ,,
A.O.C.	1·9 to 3·5 ,,	0·5 ,,

It was doubtful whether slight tetany was present in the denervated limb or not.

Another case was seen in both phases. The left radial and ulnar nerves had been severed. On the second day latent tetany was doubtful, by the criterion of the hind-limb kathodal opening current threshold (1·5 ma.). The reactions in the fore-limbs, however, showed a fall which has never been found on the denervated side on the second day in the absence of tetany.

TABLE V. (2ND DAY.)

	Left (denervated)	Right
K.C.C.	0·5 ma.	0·29 ma.
K.O.C.	0·15 ,,	1·2 ,,
A.C.C.	0·3 ,,	0·75 ,,
A.O.C.	0·22 ,,	0·45 ,,

It will be noted that the K.O.C., in particular, is lower in the denervated limb than in the limb simply affected by tetany.

On the fourth day, the normal fore-limb and hind-limb showed fully developed tetany reactions. On the ninth and twelfth days latent tetany was still present, the readings for the latter day being :—

TABLE VI. (12TH DAY.)

	Left (denervated)	Right	Hind-limb
K.C.C.	0·1 ma.	0·4 ma.	
K.O.C.	0·3 ,,	0·45 ,,	0·5 ma.
A.C.C.	0·2 ,,	0·9 ,,	
A.O.C.	0·2 ,,	0·7 ,,	

Here the readings of K.O.C. are lowered on each side to a level characteristic of tetany.

On the fourteenth day, however, though tetany was still present, the reactions in the fore-limbs showed a rise in threshold on the denervated side.

TABLE VII. (14TH DAY.)

	Left (denervated)	Right
K.C.C.	0·98 ma.	0·2 ma.
K.O.C.	1·0 ,,	0·29 ,,
A.C.C.	1·3 ,,	0·85 ,,
A.O.C.	1·3 ,,	0·21 ,,

In a further case, in which tetany developed only four and a quarter hours after sciatic section, not only did hyperexcitability occur on the denervated side, but the K.O.C. was peculiarly low (0·075 to 0·09). In this case clonic and fibrillary tetany were definitely present on the denervated side, though less active than on the normal side.

These results suggest an exaggeration of the electrical hyperexcitability of tetany in the early stages (first few hours) of degeneration of a peripheral nerve. After the phase of degenerative hyperexcitability has set in, however, no further fall of threshold occurs with the onset of tetany, the threshold even tending to rise on this event. These findings are summarized in Table VIII.

TABLE VIII.

Dog	Time after section	K.O.C. before tetany	K.O.C. in tetany	Rise or fall	Presence of tetany locally
1.	4¼ hours	1·75 ma.	0·09 ma.*	Fall (exag.)	Yes
6.	2nd day	5·0 to 10·0 ma.	0·5 ,,	Fall	?
3.	3rd day	2·0 to 4·4 ,,	0·25 ,,	Fall	—
3.	17th day	0·3 to 0·8 ,, †	0·9 ,,	Slight rise	No
6.	22nd day	0·075 to 0·25 ,, †	0·45 ,,	Rise	No

* Later 0·075, the opposite intact side being 0·25.
† Since onset of hyperexcitability on 5th day.

The progress of the changes from the 2nd to the 14th days can be followed in one animal :—

TABLE IX.

Day after denervation	K.O.C. normal side	K.O.C. denervated side	Tetany	Criterions of tetany
2nd	1·2 ma.	0·15 ma.	Not definite	Hind leg K.O.C. 1·5 ma.
9th	—	0·1 ,,	Not definite	—
12th	1·5 ,,	0·2 ,,	Latent	Hind leg K.O.C. 0·5 ma.
14th	0·29 ,,	1.0 ,,	Latent	Hind leg K.O.C. 0·32 ma.

Summary and Conclusions.

(1) Peripheral nerve sections were undertaken in seven dogs, and parathyroid tetany induced. Observations both upon the incidence of tetany and upon the electrical reactions were made.

(2) Clonic and fibrillary tetany can occur in muscles denervated a few hours previously (four and a quarter hours in these experiments).

(3) Fibrillary tetany can occur for at least twenty-four hours after denervation.

(4) Tonic tetany has not been observed after denervation.

(5) After the third day following denervation no elements of tetany have been detected. Observations have been continued as far as the twentieth day.

(6) The hyperexcitability to electrical stimuli which occurs in tetany is present to an exaggerated degree for some hours after denervation (forty-eight hours in the experiments). A second phase is subsequently found in which the electrical reactions of denervated muscle do not fall, but rather tend to rise with the onset of tetany.

Part II.

Tetany in "Spinal" Dogs.

Complete transection of the spinal cord in the region of the eighth dorsal segment was performed on six dogs. A seventh was subjected to transection at the level of the first dorsal segment. Parathyroid tetany was induced at varying periods after transection. Eleven observations upon the effect of tetany on the regions posterior to the section were made at intervals varying from six hours to thirty-six days. In addition, the effects of tetany upon the properties of the spinal preparations were examined. These observations are summarized in Table X.

TABLE X.

Dog	Time after spinal section	Tetany in normal fore-limbs	Tetany in hind-limbs	"Spinal" reflexes
1.	6 hours	Fibrillary only	Tonic (extensor), clonic and fibrillary	+ +
2.	30 hours	Fibrillary and slight clonic	Absent	(T.R.)
3.	5 days	(1) Tonic, fibrillary, slight clonic	Absent.	+ +
		(2) Tonic and fibrillary	? Spontaneous clonic	+ +
4.	6 days	—	Fibrillary only	+
4.	7 days	Fibrillary and clonic	Fibrillary and clonic	+
2.	8 days	Fibrillary only	Absent	(T.R.)
4.	11 days	Clonic and fibrillary	Clonic, fibrillary, occasionally tonic	+
4.	13 days	Clonic	Clonic	+
5.	14 days	Tonic, clonic, fibrillary	Tonic, clonic, fibrillary	+
4.	18 days	Occasional clonic	Occasional clonic	+ + § 1
6.	36 days	Tonic, clonic, fibrillary	Tonic, clonic, fibrillary	+ + § 2

\+ = Present.
\+ + = Very active.
§ 1 = Added reflexes.
§ 2 = Added reflexes.
T.R. = "Spinal preparation" reflexes absent, but tendon reflexes present.

Analysis of Table.

(1) *Occurrence of Tetany.*—Tetany was absent on three observations only out of eleven. On one of these occasions tetany was doubtfully present on the same day. The negative results bear no constant time relationship to the transection of the spinal cord, occurring as they do at thirty hours, five days and eight days after section. Tetany was present at six hours, six days and seven days after section. Two of the negative observations were on the same dog (Dog 2), in which active tetany was poor, fibrillary and slight tonic tetany being present on the occasion of the first observation (thirty hours), and only fibrillary tetany on the second occasion (eight days). Unlike the other five animals of the series, this dog never developed the characteristic reflexes of the chronic spinal preparation, though the tendon reflexes were present from the first day after section. Further, the general condition of this animal was poor throughout, and especially so on the eighth day. It may be said, therefore, that in this series of "spinal" dogs tetany was definitely present on eight occasions out of eleven, and that in two of the three exceptions more than one factor was present which might render the one dog concerned an unfavourable subject.

The remaining exception (Dog 3, fifth day) requires further consideration. Parathyroidectomy was performed on the fourth day after

transection of the cord. On the fifth day the following notes were made :—

11.30 a.m.: Lower limbs in posture of semi-flexion, slight resistance to passive flexion. Knee-jerks and ankle-jerks present and equal. Deep pressure on pad of foot produces a strong flexion reflex with crossed extension. Passive flexion produces crossed extension. Anal reflex present. No reflex stepping.

Upper limbs: Bilateral extensor rigidity. Resistance to passive flexion, sometimes modified when the "clasp-knife" phenomenon is shown. Fibrillary twitches and occasional clonic tetany in fore-limbs and scalp.

3.15 to 4 p.m.: Continuous fibrillary tremors in both fore-limbs; none in hind-limbs. Fibrillary twitches in trunk, extending posteriorly to about as far as, but not further than half way down, the scar of the spinal operation. During the forty-five minutes of observation two rapid flexion movements occurred in the left hind-limb. At the first of these there were flies round the limb, at the second it appeared as if the flexors of the thigh had twitched spontaneously. Apart from this no spontaneous movements of any kind were seen in the lower limb during this period.

There was thus tonic, clonic and fibrillary tetany in the forepart of the body during the morning, and fibrillary tetany in the same areas continuously for forty-five minutes during the afternoon. On neither occasion was any element of tetany observed in the posterior portion of the animal, despite considerable activity of the "spinal preparation" reflexes.

The eight occasions (four dogs) on which tetany occurred in the areas below the spinal section may now be discussed.

Dog 1.—Parathyroidectomy had been performed two days before transection of the cord was undertaken. Six hours after transection the following was noted: Fibrillary tetany in the muscles of the left shoulder and fore-limb. In the left hind-limb, occasional bouts of definite clonic tetany occurred combined with strong extensor tone. Right hind-limb, occasional bouts of clonic tetany were seen. In this dog the "spinal preparation" reflexes, which are discussed fully later in this paper, were very active at this stage.

Dog 4.—Tetany occurred on the sixth, seventh, eleventh, thirteenth and eighteenth days after transection. In all instances it was present in the hind-limbs and there was apparently no significant difference between the severity in fore and hind limbs. "Spinal" reflexes varied in activity, but were always present.

Dog 5.—All three elements of tetany were present in the hind-limbs on the fourteenth day after transection. The "spinal" reflexes were poorly developed in this case.

Dog 6.—Tetany was precipitated on the thirty-sixth day after transection. It occurred in all its forms in the hind-limbs, but with less extensor rigidity than in the fore-limbs. "Spinal" reflexes were very active throughout in this case.

(2) *Nature of tetany in "spinal" dogs.*—Parathyroid tetany in its three forms, tonic, clonic and fibrillary, has been observed in "spinal" dogs at various periods after cord transection.

Tonic tetany has been observed six hours, fourteen days and thirty-six days after transection. On only two occasions was this form of tetany present in the fore-limbs and absent in the hind-limbs, and on one occasion this finding was reversed. The posture seemed to be almost invariably extensor, and there did not appear to be any essential difference between tonic tetany in neurologically normal dogs and in acute or chronic "spinal" dogs.

Clonic tetany has been seen six hours, seven days, eleven days, thirteen days, fourteen days and thirty-six days after spinal transection. On only one occasion was clonic tetany present in the fore-limbs and absent in the hind-limbs, and on one other occasion this finding was reversed. In Dogs 1, 4, 5 and 6 the clonic twitches which occurred closely resembled those of tetany in a normal dog. In Dog 4, however, "The clonic extensor-jerks are slower than in tetany in normal animals, the period of contraction being extended to about half a second." Myotatic irritability and considerable excitability of "spinal" reflexes were present at the time. The case is discussed fully at a later stage in this paper.

Fibrillary tetany differed in no visible manner from that occurring in areas possessing a normal nerve supply.

On the whole there was a tendency for each type of tetany to make itself manifest earlier in the normal fore-limbs than in the "spinal" hind-limbs. In one or two cases tetany was more active in the normal than in the abnormal limbs, but on the whole this distinction was by no means obvious. In Dog 6 (thirty-sixth day) tetany was more pronounced in the fore-limb, while in Dog 1 (six hours) it was more active in the hind-limb.

(3) *Spinal preparation reflexes in tetany.*—The presence and form of the various reflexes associated with the spinal mammalian preparations were studied in conjunction with the variations occurring when tetany supervenes. Only one dog (Dog 2) failed to develop any of the reflexes. The dog was kept for nine days after transection of the cord. Parathyroidectomy was performed on the day prior to the transection. Tetany occurred thirty-hours and eight days after the spinal operation. Twenty-six hours after section and just prior to the onset of tetany the knee-jerks were both very active. At the onset of tetany (thirty hours) and on subsequent days the hind-limbs remained flaccid, the knee-jerks

were present but not very active, and on no occasion were any added reflexes present. This dog did not develop tetany in the hind-limbs. The remaining dogs may be taken in order.

Dog 1.—No observations were made before the onset of tetany. At the onset of tetany (six hours) the knee-jerks were present and exaggerated. In addition: (1) squeezing the pad of the left foot produced extension—not flexion—of that leg, a violent rapid thrust; (2) squeezing the pad of the right foot produced characteristic homolateral flexion and crossed extension; (3) there was a strong extensor posture present on account of the tetany. It is interesting to record the presence of a well-marked crossed extensor reflex within six hours of transection of the cord.

Dog 3.—No observations were made before the onset of tetany. At the onset of tetany (five days), the knee-jerks were present and equal. The posture of the hind-limbs was one of semi-flexion. Slight resistance to passive flexion was encountered. Deep pressure on the pads of the feet produced a strong flexion reflex with crossed extension. The anal reflex was present. There was no tetany in the hind-limb at the time of making this record. The fore-limbs showed bilateral extensor rigidity, resistance to passive flexion being of the "clasp-knife" type. Fibrillary and clonic tetany were present.

Dog 4.—Before parathyroidectomy, on the third day of section, the knee-jerks were exaggerated on both sides. Signs of flexion and of crossed extension reflexes were present. Twenty-four hours after parathyroidectomy, in the presence of electrical hyperexcitability, but seven hours before the appearance of active tetany and on the sixth day of section, the knee-jerks and flexion and crossed extension reflexes were present, but not very active.

At the onset of active tetany knee-jerks very brisk, fibrillary tetany in right hind-limb. Seventh day after section knee-jerks exaggerated, limbs flaccid: flexion and crossed extension reflexes present, but not very active. Fibrillary tetany was present. Subsequently the activity of the tetany was enhanced by heat when apparently spontaneous movements of the following nature were observed: (*a*) Flexion and extension of the left ankle occurring two or three times. The movement appeared co-ordinated and it was slow and deliberate in nature, occupying about half a second. This was followed by (*b*) spontaneous bilateral extension of both hind-limbs upwards, against gravity, the dog being upon his back at the time. The left leg extended first, both resisted passive flexion and remained extended for some moments. At this time the fore-limbs were not rigid, only fibrillary tetany being present. Subsequently (*c*) flexion which appeared to be active occurred and both limbs remained flexed. Later on the same day these three phases were repeated, the right ankle now moving before the left. The knee-jerks were extremely active and the flexion reflex much more brisk than heretofore. Phillipson's reflex was active.

On the tenth day, when active tetany was not present, the flexion and crossed extension reflexes were obtained, but had lost a great deal of their

activity. On the eleventh day, when tetany had again been enhanced by heat, spontaneous movements were again present, smooth extension against gravity being repeatedly observed. On the twelfth day an increase of the briskness of both flexion and crossed extension reflexes occurred without activation of tetany. On the thirteenth day active tetany spontaneously returned. It was clonic in form. The "spinal" reflexes were again very active; the crossed extension reflex varied from its usual form in that passive flexion of one leg led to repeated flexion and extension of the opposite leg.

Dog 5.—Before parathyroidectomy, on the third day after section, both knee-jerks were obtained, but no added reflexes and no spasticity were present. On the fifth day slight spasticity occurred and both flexion and crossed extension reflexes were obtained. On the sixth day the response to the flexion and the crossed extension reflexes was sluggish and prolonged. On the eleventh day flaccidity had occurred and the "spinal reflexes" were feeble. On the twelfth day both flexion and crossed extension reflexes were absent; the hind-limbs were flaccid and the knee-jerks not exaggerated. On this day parathyroidectomy was performed.

Two days after parathyroidectomy clonic tetany appeared in the scalp and fore-limbs. The knee-jerks had become brisk. Great myotatic irritability (to be referred to subsequently) occurred in the hind-limbs. The flexion and crossed extension reflexes returned though they were not active. Spontaneous micturition reflexes occurred, the two hind-legs flexing simultaneously, micturition occurring and bilateral extension of the hind legs following. A few hours subsequently spontaneous flexion and extension occurred in the hind legs, both legs being rigidly extended, then one flexing and remaining flexed. The crossed extension reflex was present but was distorted. Passive flexion of the right leg produced extension of the left leg while passive flexion of the left leg led repeatedly to flexion of the right leg.

Dog 6.—Before parathyroidectomy this dog was observed from the fifth to the thirty-fourth day. On the fifth day the knee-jerks were obtained and there was slight spasticity. The crossed extension reflexes were present and equal. On the seventh day spasticity had increased and this continued to increase subsequently. On the nineteenth day the knee-jerks were very brisk, the flexion reflex was present, but sometimes irregular, a rapid jerk to half-flexion being followed by a much slower completion of the movement. On the twentieth day, passive flexion of one leg was found sometimes to excite extension and sometimes flexion of the other. Pinching the toes of one leg excited flexion on that side, then opposite extension, followed by a reversal of the movements, a marching reflex. On occasion passive flexion of one leg excited a series of extensor thrusts on the opposite side, a crossed pawing reflex.

Parathyroidectomy was performed on the thirty-fourth day. A few hours prior to the onset of active tetany the distribution of tone in the hind legs enabled the dog to stand on all four legs for several seconds.

After the onset of tetany the following observations were made:—

(1) When the dog was held up spontaneous pawing and marching reflexes were constantly repeated, continuing actively for minutes at a time. The activity of these movements had never been approached before the onset of tetany.

(2) The dog "marched" and "pawed" even when lying on his side.

(3) The crossed extension and the flexion reflexes, elicited in the usual way, produced violent jerked movements, much more rapid and active than before tetany.

(4) *Electrical reactions in tetany in "spinal" dogs.*—Stimulation was with a small electrode applied to the skin over the muscles to be tested, a large indifferent electrode being applied to a distant part of the body. The circuit described elsewhere was used [7]. No significant alteration of threshold occurred in the hind-legs as a result of transection of the spinal cord; a tendency towards higher readings in the hind-limb is found under normal conditions. With the onset of tetany, at whatever period after transection this occurred, the electrical thresholds fell coincidently in the fore and hind limbs to the usual degree, the kathodal opening contraction being in the region of one-tenth its normal value.

(5) *Other observations on tetany in "spinal" dogs.*—In observing the phenomena of tetany in these six "spinal" dogs certain matters of interest, some confirmatory of previous observations, others seen for the first time, were recorded.

(*a*) *The effect of heat.*—A dog in latent tetany can frequently be thrown into active tetany by exposing it to heat just sufficient to cause panting [10]. Perhaps an added alkalosis is responsible for this. If fibrillary tetany is present before heating, well-marked clonic or tonic tetany can usually be induced within five minutes of the dog commencing to pant. Cooling the animal removes the symptoms coincidently with the cessation of panting. In one or two instances, inhalations of oxygen containing 10 per cent. of carbon dioxide relieved the tetany within a few minutes.

But in addition to the effect of heat upon the animal as a whole, radiant heat from an electric radiator exercised an effect upon the muscles irradiated. This effect appeared to be either peculiar to, or very much more pronounced in, the "spinal" hind-limbs, in contradistinction to the normally innervated fore-limbs.

Dog 4.—The dog was in fibrillary tetany. When a hind-limb was irradiated the muscles became very sensitive to touch. A light tap on a flexor of the knee would produce contraction locally, flexion of the knee and a movement of the tail. No such effect was present in the fore-limbs and it was also absent

in the opposite hind-limb which was kept cool. This observation could be repeated alternately in the two hind legs by turning the dog over from side to side. Finally a touch would cause the whole limb to jerk and the tail to twitch, while the reflexes and the myotatic irritability were not changed in the front leg in response to similar treatment. The flexion reflexes were present, but not very active at this time.

(*b*) *Myotatic irritability in tetany.*—In addition to this myotatic irritability produced by heat, the muscles of a dog in tetany are hyperexcitable to mechanical stimuli, apart from heat. Very active fibrillary contractions occur on cutting such muscles with a knife. This had previously been noted in the case of the scalp muscles in decerebrating a dog in tetany. It was confirmed in the muscles of the "spinal" preparation.

(*c*) *Increased response of muscle to mechanical excitation of nerve.*—In one dog of the series (No. 4) the sciatic nerve on the left side was exposed during mild active tetany. It was found that digital manipulation of the nerve excited extensor twitches in the opposite leg and foot. No movement occurred on the side stimulated. The nerve was merely rolled under the finger, and each roll produced a definite rapid extension. The right sciatic was exposed, and a similar crossed reaction noted. The possible analogy between this observation and Chvostek's sign is interesting.

(*d*) "*Spontaneous*" *movements.*—These have been recorded above (Dogs 4, 5, 6). In all three cases the movements occurred at a time when the "spinal" reflexes were unduly brisk, and in Dog 6 movements were performed analogous to the "marching" or "pawing" reflex. The general nature of these movements and the associations mentioned above perhaps make it probable that they were in reality reflex movements set in motion by a small peripheral stimulus.

Summary.

(1) Tetany can occur in "spinal" dogs. It was observed at intervals of from six hours to thirty-six days after mid-dorsal section in five out of six dogs. In a further experiment in which transection was undertaken at the level of the first dorsal segment, tetany occurred in all four limbs.

(2) Tetany in "spinal" dogs occurs in all its three types, tonic, clonic and fibrillary. This is true whether the section be high or low in the dorsal region.

(3) The clonic contractions of tetany tend to be less rapid in the hind-limbs of the "spinal" animal.

(4) In "spinal" dogs the activity of the tetany produced does not appear related to the time of its occurrence after transection of the cord.

(5) The peculiar reflexes of the "spinal" animal were present as early as six hours after transection, when tetany occurred at that time. The activity of the "spinal" reflexes tended to increase with the onset of tetany. "Spontaneous" co-ordinated movements occurred in the hind-limbs. There were distortions of the typical "spinal" reflexes.

(6) The myotatic irritability of tetany is retained in the hind-limbs of the spinal preparation. Myotatic irritability induced by heat was greater in "spinal" than in normally innervated limbs.

Part III.

De-afferentation and Tetany.

The interruption of the afferent nerve supply from one or both hind-limbs was undertaken in four dogs.

The dorsal spinal roots were severed extrathecally, the ventral (motor) roots being left intact. The operation was performed in the lumbar region, on one side in the case of three dogs, and bilaterally in one. In one case decerebration was subsequently performed. Tetany was induced by removal of the thyroid and parathyroid glands, at times

TABLE XI.

Dog	Region de-afferented	Onset of tetany	Condition of affected limb	Control	Condition of control
1.	Left L. 4, 5, 6, 7 and decerebrate	2½ hours	Flaccid. Fibrillary tetany in hamstring	Opposite leg	Decerebrate rigidity
				Fore-limbs	Decerebrate rigidity and clonic tetany
2.	Left L. 4, 5, 6, 7	Some days	No tetany	Opposite leg	Slight clonic tetany
3.	Left L. 4, 5, 6, 7, 8	2½ days	Fibrillary tetany hamstring	Opposite leg	Clonic tetany hamstring
		3 days	Slight clonic ankle and knee. Flaccid	Opposite leg	Active clonic tetany. Clasp-knife rigidity
4.	Left and rt. L. 2, 3, 4, 5, 6, 7, 8 and cut cauda equina	12 hours	Fibrillary left gastroc., left hamstring, right glutei	Fore-limbs and trunk	Fibrillary occasional clonic
		36 hours	Fibrillary, both hind legs	Fore-limbs and trunk	Indifferent fibrillary tetany
		60 hours	Flaccid. Continuous fibrillary	Fore-limbs and trunk	Strong tonic extensor tetany. Continuous, violent clonic and fibrillary tetany

varying from a few hours to three days after the spinal operation. The result of de-afferentation upon tetany is shown in Table XI.

Dog 1.—In this case the left hind-limb was de-afferented by section of the dorsal roots of the 4th, 5th, 6th and 7th lumbar spinal nerves. The animal was in slight tetany at the commencement of and during the operation. Intercollicular decerebration was undertaken immediately after de-afferentation, fibrillary tetany being present in the scalp muscles during its execution. Two and a half hours subsequently, the decerebrate preparation was found to be satisfactory. Decerebrate rigidity was present in the three untouched limbs. Tonic extensor rigidity was very great. No clonic or fibrillary twitches could be seen in these limbs until flexion was undertaken, when both fore-limbs showed clonic jerks. The de-afferented limb was flaccid, but fibrillary tetany was present in the hamstring muscles.

Dog 2.—The area de-afferented corresponded with that in Dog 1. Decerebration was not performed. Subsequently, clonic tetany induced by parathyroidectomy occurred in the fore-limbs and head, and to a less degree in the right (normal) hind-limb. It was entirely absent in the left (de-afferented hind-limb). Tonic and fibrillary tetany did not occur in this dog.

Dog 3.—The dorsal roots of lumbar 4, 5, 6, 7, 8, on the left side were divided. On the third day clonic tetany occurred in the left shoulder region and in the right hind-limb, both in extensor and flexor muscles. One or two twitches were seen in the hamstring muscles of the left hind-limb. In addition, fibrillary tetany was observed in the region of the left ankle. A few hours later very active clonic and fibrillary tetany occurred in both fore-limbs. The dog was placed in a position of dorsal decubitus and the two hind-limbs compared. The right showed very active clonic tetany of the hamstrings, knee extensors and flexors, with short sharp twitches of the flexors and extensors of the pad of the foot; there was also general extensor rigidity. The left (de-afferented) showed slight clonic tetany of the hamstrings, flaccidity of the knee extensors, with occasional added jerks. Very occasional twitches were seen in the ankle extensors and flexors. Contraction of the flexors of the pad of the foot were small (fibrillary) but active. These contractions were of longer duration than those of the right side. The limb as a whole was flaccid.

Dog 4.—The dorsal roots of lumbar 2, 3, 4, 5, 6, 7, 8, were severed on both sides, and the cauda equina cut through below L8. Tetany was precipitated twelve hours after the operation. There were occasional clonic muscular contractions in the fore-limbs, and definite fibrillary tetany, without clonic jerks, in the gastrocnemius muscle of the left hind-limb. Subsequently fibrillary tetany was observed in the muscles of the shoulder and back, in the right gluteal and left hamstring or gastrocnemius muscles. There was occasional clonic jerking in the fore-limb but none in the hind-limb. At thirty-six hours there was definite fine fibrillary tetany in the extensors of the right hip, and in the right and left gastrocnemius. After sixty hours, in head, violent clonic tetany: fore-limbs in continuous tonic extension, very difficult to

overcome by passive flexion; continuous additional clonic jerks of violent nature; fibrillary tetany; trunk and shoulders, active clonic fibrillary tetany; remainder, fibrillary tetany only. Hind-limbs completely flaccid throughout; no clonic tetany whatever; continuous fibrillation throughout the musculature of both hind-limbs. The phenomena were observed continuously for fifteen minutes. Later in the third day, clonic tetany occurred in the fore-limbs, but was entirely absent from the hind-limbs.

Analysis of Results.

Of the four dogs, three showed fibrillary tetany in the de-afferented limb. In the one failure tetany was but slight in the opposite control limb. In Dog 1, decerebration did not modify the findings. In Dog 3, on one occasion twitches amounting to clonic tetany were seen in the hamstring muscles of the de-afferented side. With this exception, the tetany observed in de-afferented areas was always fibrillary. In all tetany of this type was observed on five separate occasions, on each of which well-marked tonic or clonic tetany was present in the control limbs. In the case of Dog 4, the contrast between the fore-limbs and the hind-limbs was most strongly marked on all occasions. In this case both hind-limbs had been de-afferented.

Conclusion.

De-afferentation of one or both hind-limbs greatly reduces the activity of tetany. With one temporary exception, in which clonic tetany occurred, the form of tetany in de-afferented muscles has always been fibrillary.

THE WORK AND OPINIONS OF PREVIOUS WRITERS IN RELATION TO THE PRESENT RECORDS.

(1) *Denervation and tetany.* — Paton, Findlay and Watson [1] recorded that peripheral nerve section abolished all "spasms, tremors and jerkings" of tetany. This I found true for fibrillary tetany only if an interval of some twenty-four hours is left for certain unknown peripheral changes to follow upon nerve section.

(2) *Tetany in spinal dogs.*—Carlson and Jacobson [4] found that after high thoracic transection of the cord "extreme parathyroid tetany (epilepsy) does not directly involve the part posterior." In view of this statement, I made a spinal preparation with the transection at the level of the first dorsal segment. Very active tonic, clonic and fibrillary tetany occurred in all four limbs. Luckhardt, Sherman and Serbin [5] mentioned that in chronic spinal preparations, while clonic and fibrillary

tetany are active, tonic tetany is less pronounced below the level of the section, and when present is "in a great measure due to the stimulation of sensory nerves of some part of the animal posterior to the transection." My records show that sometimes the fore-limbs and sometimes the hind-limbs show the more active tonic tetany. The view that the tetany, both tonic and clonic, is contributed to by sensory impulses is supported by its abolition by de-afferentation. Mustard [2] also states that the epileptic (*sic*) spasms of parathyroid tetany do not develop posterior to a spinal transection, and regards this as evidence of a dependence of tetany upon certain higher centres. I was unable to find a constant difference between the manifestations of tetany above and below the level of spinal sections.

(3) *Spinal reflexes and tetany.*—Luckhardt, Sherman and Serbin [5] recorded the great increase in reflex irritability of spinal dogs in tetany. They also noted the reduction in the period of spinal shock. Further, they noted the appearance of new and unusual reflexes. They state that animals in tetany were hypersensitive to strychnine. Carlson and Jacobson [4] mention reflex hyperexcitability as a feature of tetany. These observations were confirmed, with the exception of the strychnine effect, which was not examined.

(4) *Tetany and de-afferentation.*—Mustard [2] records de-afferentation of one hind-leg as leaving "slight twitchings" when tetany supervenes. This coincides with my observations.

(5) *Hyperexcitability of peripheral nerve trunks.*—Falta [11] quotes von Frankl-Hochwart to the effect that Trousseau's phenomenon depends upon the excitability of the nerve trunks themselves, and that tetany can result bilaterally from pressure on one brachial plexus. He further quotes Schlesinger as saying that only "mixed nerves" containing sensory fibres can excite tetany. These observations are of interest in association with my finding of contractions of the opposite leg on mechanically stimulating the exposed sciatic nerve in a spinal preparation. I cannot offer an explanation of this phenomenon.

Summary.

(1) The lowest reflex spinal arc is requisite to the full muscular manifestations of canine parathyroid tetany. If this arc be interrupted on its afferent side by dorsal root section the grouping and synchronization of the contractions are minimal, and *fibrillary* tetany results. But if the arc remain intact, the contractions of the fibres are either synchronized into violent clonic muscular jerks (*clonic* tetany) or show

maintained contraction (*tonic* tetany). Both types of contraction may occur contemporaneously in the same limbs, and clonic jerks may be present in a muscle which exhibits tonic tetany (Parts I and III).

(2) All the elements of tetany are retained in the hind-limbs when the spinal cord has been transected in the cervical or dorsal region. It is not found that impulses from higher centres add anything to the pattern of canine tetany. Tetany shortens the period of "spinal shock" and increases the activity of "spinal" reflexes. The myotatic irritability of the transverse spinal preparation is also increased by tetany (Part II).

(3) Fibrillary tetany is tetany in its simplest form. While an intact spinal-cord reflex arc is essential to the development of the clonic and tonic forms of tetany, fibrillary tetany persists if the motor connections between the spinal cord and the muscle remain intact. Muscles which have been completely denervated for a few days do not develop fibrillary tetany (Part I).

(4) Fibrillary tetany is not abolished by denervation until about twenty-four hours after section of the nerve of supply; thenceforward it is entirely absent. This implies that fibrillary tetany depends upon a circulatory factor acting upon an intact peripheral mechanism, the function of which is critically altered, not at the time of nerve section, but some twenty-four hours subsequently (Part I).

(5) The electrical hyperexcitability which characterizes muscles in tetany is exaggerated in the early stages (first few hours) after section of the nerve of supply. On about the fifth day after section an independent electrical irritability characteristic of denervation sets in. At this stage tetany does not lower the electrical threshold, but rather tends to raise it (Part I).

Conclusions.

The essential feature of tetany appears to be the action of a circulatory factor peripherally upon some site in the muscle, to cause repeated contractions of individual muscle fibres and electrical hyperexcitability. Both this fibrillary tetany and the electrical hyperexcitability are influenced by the nerve supply from the central nervous system. Given the integrity of the spinal reflex arc, the muscular contractions are synthesized into the characteristic forms of "tonic" and "clonic" tetany. In the presence of only the motor supply from the spinal cord the contractions remain fibrillary in type, but electrical hyperexcitability persists. Complete denervation leads to the following

sequence of events: At first there is continuation of fibrillary tetany and increased electrical excitability with the onset of tetany. This probably corresponds to a phase of early degeneration at some point of action within the muscle which maintains its irritability to the circulatory factor of tetany, and increases the normal effect of the latter on direct electrical excitability. Subsequent degenerative changes lead successively to the loss of the fibrillary response to the circulatory factor and the institution of a peculiar electrical excitability of degeneration which is independent of tetany.

If this interpretation is correct, parathyroid tetany arises essentially from the action of a changed circulation upon muscles. The point of action depends upon an intact motor nerve supply for its function, and undergoes successive changes of threshold on denervation. An intact spinal reflex is required to convert essential or fibrillary tetany into its elaborate clonic and tonic forms. Impulses from nervous centres higher than the spinal cord are not requisite to these forms of canine tetany.

Neither the effects of tetany on conduction through the central nervous system itself, nor the nature of the circulatory changes acting peripherally, have been studied.

The "final common point" in muscle excitation.—If the foregoing interpretation of the neuromuscular mechanism of tetany be accepted, this disease draws attention to an interplay of nervous and circulatory factors to produce effects at what might be called a "final common point" of synthesis of influences affecting muscular contraction. Other examples of the twin importance of circulatory and nervous factors in affecting this final point of stimulation of muscle are the actions of circulating drugs in enhancing, depressing or modifying the effects of nervous stimulation (e.g. the selective peripheral actions of curare [12] and physostigmine [13]) on the one hand, and, on the other, the effect of denervation on the response of muscle to drugs (e.g. acetyl choline [14]).

Diseases other than tetany, in which altered circulatory states might diminish or increase the effect of nervous stimulation of muscles, are not discussed in this paper.

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LOCALIZATION OF THE SLEEP MECHANISM[1].

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Introduction.

The value of hypersomnolence as a localizing symptom is still somewhat uncertain. The determination of this point, as well as the understanding of the mechanism of pathological and normal sleep, may obviously be greatly furthered by the investigation of cases of brain tumour associated with disturbances of the sleep rhythm. For these reasons the present clinico-pathological study of three cases of diencephalic tumour has been undertaken. In two of these hypersomnolence was a prominent clinical feature, while the third, in which there was no sleep disturbance, is included for purposes of control and comparison.

To provide a basis for the evaluation and discussion of the cases a brief review of some of the concepts of normal and pathological sleep and of the evidence upon which these concepts are based seems advisable.

Normal Sleep.

Normal sleep, Kleitman [1] believes, is characterized by three criteria: (1) a loss of critical reactivity to events in the environment, (2) an increased threshold of general sensibility and reflex irritability, and (3) an ability of being aroused or brought back to wakefulness. Trömner [2] defines sleep as a primitive, periodic, instinctive life process which can be aroused by many different means, and which serves to rest the cerebrum while permitting bodily regeneration and growth. Pette [3, 4] regards the sleep-wake rhythm as an elementary vegetative process necessary to life and similar to temperature regulation or water metabolism. All writers agree that the exact nature of the sleep process is still unknown, but certain characteristics of normal sleep

[1] Read in abstract before the Philadelphia Neurological Society, April 27, 1934.

have been observed and form in part the basis for such definitions as are given above. It has been pointed out (Trömner [2]) that the phenomena occurring during sleep may be grouped as follows: (1) autonomic effects, such as a slight rise of temperature, lowering of blood-pressure, sweating, slowing of the pulse, lowering of the metabolic rate: (2) "active" or stimulatory effects, including myosis, changes in the position of the eyes, yawning; (3) inhibitory effects, particularly mental and emotional inhibition, and the slowing of some of the secretory activities; and (4) dissociation effects, such as dreams, and the changes associated with partial awakening. It is well established that sleep is influenced by a great variety of factors, including afferent exogenous stimuli, cortical processes, endocrine changes and activity of the autonomic system. On the basis of such knowledge it has seemed probable to many writers that a central control for the sleep-wake rhythm exists, and from the apparent similarity of the process to known vegetative functions which are closely related to the interbrain it has seemed reasonable to many to postulate a sleep centre in the diencephalon.

Finally, experimental and clinical experiences have done much to confirm this conclusion reached on theoretical grounds. It has been shown by Karplus [5] that in decerebrate animals the normal sleep rhythm is preserved. Lesions of various types located in the diencephalon or mesencephalon has been found associated with hypersomnolence. Experimental damage and experimental stimulation of portions of the interbrain have produced abnormal sleep states in animals. The rather localized effect of certain soporific drugs upon the interbrain has been demonstrated. These data, even though dealing with excessive sleep for the most part, have resulted in the obvious inference that any area controlling pathological somnolence must also play an important role in the normal sleep rhythm, and they consequently form an important part of our knowledge concerning sleep.

Review of the Literature.

A survey of the previous reports related to sleep disturbances associated with cerebral lesions tends to be somewhat confusing, due largely to the rather wide disagreement as to the exact localization of the central sleep-controlling mechanism. It seems probable that some of the divergence of opinion may be the result of difficulties in the selection of clinical cases of hypersomnolence. A truly hypersomnolent individual not only sleeps a greater portion of the twenty-four hours

than the average but falls asleep in the presence of stimuli, such as conversation, reading and even eating, which ordinarily maintain a waking state. Furthermore, the sleep is always characterized by its reversibility, i.e. the ability to be aroused to a state of essentially normal mental and physical capacity by stronger stimuli, such as calling by name, shaking, or questions. As a further explanation of the differing opinions of various workers there are certain additional factors inherent in the different approaches to the problem. Following a survey of the evidence relating to hypersomnolence these may be considered in presenting a brief summary of the previous work on the subject.

It is convenient to consider the work of other writers in three groups, based upon the type of pathology involved: (1) inflammatory, (2) neoplastic, and (3) experimental lesions. It is true that traumatic, degenerative and vascular changes associated with hypersomnolence have been reported (Stertz [6]), but since none of this group of cases has been of importance in the closer localization of the sleep mechanism, they will not be considered here.

(1) *Inflammatory lesions of the brain associated with hypersomnolence.*—Mauthner [7] (1890) was among the first to suggest that the diencephalon exerted a control over sleep, this conclusion being based upon his observation that the majority of the pathological changes in the brain of an encephalitic patient who had shown hypersomnolence lay in the interbrain. Similar studies on many more cases, seen in the early years of this century and subsequent to the influenza epidemics of 1918 and 1920, led Economo [8] to essentially the same conclusion. He went further however and postulated a central sleep mechanism occupying the gray matter about the caudal portion of the third ventricle and the rostral end of the aqueduct, lying close to the nucleus for the third nerve ; he emphasized the frequency with which sleep disturbances and abnormalities of the oculomotor nerve form the principal symptoms of epidemic encephalitis.

In addition to these studies of encephalitis a number of reports of purulent collections and of meningitis have appeared. Luksch [9] (1924) tended to confirm the opinions of Economo, in reporting a case of subacute bacterial endocarditis with hypersomnolence, in which autopsy revealed a suppurative lesion involving the posterior portion of the third ventricle and its walls, and the structures about the upper end of the aqueduct. In the same year Adler [10] found multiple abscesses in the hypothalamus and the periventricular gray matter around the

third ventricle in a very similar case. Other areas of the interbrain were implicated, however, by Hirsch [11, 12] (1924, 1928), who found, in studying four cases with sleep disturbances, lesions between the anterior and posterior commissures in one, in the pulvinar near the posterior commissure in two, and in the dorsal gray matter of the rostral portion of the aqueduct in a fourth. Still another region of the interbrain apparently related to hypersomnolence was described by Marinesco and his associates [13] (1928), who reported upon two patients suffering with tuberculous meningitis who showed excessive sleep. Subsequent pathological observations showed the tubo-infundibular region to be badly damaged—in part as the result of interference with its blood supply.

(2) *Cerebral tumours associated with hypersomnolence.* — Since Sinkler [14], in 1893, described a case of brain tumour involving the diencephalon in which hypersomnolence was a prominent symptom many similar reports (references [15] to [29] inclusive) have appeared in the literature. The early papers, based usually upon cases in which rather large tumours were found, are marred by the absence of careful description of the exact location of the lesions. Soca [15], in 1900, noted hypersomnolence in a case with a tumour in the infundibular region. On the other hand, Salmon [16] (1906) believed that the destruction of the hypophysis, or of the infundibular stalk or its connexions, was responsible for the appearance of pathological sleep in cases he observed. Other evidence seemed to point not to a single diencephalic area, but to the entire interbrain. François and Vernier [17] (1919) for example, observed a woman of 38 who suffered with marked somnolence for four months prior to her death. Autopsy revealed a large tumour, apparently originating from the base of the brain between the chiasm and the cerebral peduncles and growing upward to the corpus callosum, and lateralward to include the entire diencephalon and reach the lateral ventricles. Weisenberg [18] (1911), in reviewing all the reported cases of tumour arising within the third ventricle, noted four in which somnolence was a prominent symptom.

Fulton and Bailey [19] (1929) reported an unusual and important case. A woman of 28, who had had attacks of drowsiness for four or five years, was found at necropsy to have a small tumour (2 by 1·5 cm.) in the floor of the third ventricle involving the infundibulum at its dorsal end, almost the entire tuber cinereum and the mammillary bodies, but not encroaching upon the ventricular system sufficiently to cause intracranial hypertension. In three additional cases with hypersomno-

lence they found in one a small gelatinous cyst (17 mm. in diameter) attached to the roof of the third ventricle and lying within it; in another a solid tumour filling the ventricle, and in the third a very widespread pinealoma involving practically the entire diencephalon. In view of the varied nature of their cases as well as those in the literature these authors did not feel that it was possible to speak of a sharply localized sleep centre in the diencephalon, in spite of the clear-cut clinical picture and the sharply localized infundibular, tuber and mammillary lesion in their first case.

Additional evidence concerning the importance of various hypothalamic areas was furnished by the work of Marinesco and his associates [13, 20]. In 1929 these workers reported a comparative study of two cases with marked internal hydrocephalus, dilatation of the third ventricle and consequent lesions in the floor of the ventricle. In one of these the changes occurred in the right retro-thalamic region, beneath the corpus callosum and limbic convolution above, the cerebral peduncles in front, and extended into the cephalic portion of the mesencephalon where the gray matter surrounding the aqueduct was involved and the iter completely occluded. This patient showed marked hypersomnolence. The control case showed at autopsy a large tumour of the left cerebellar hemisphere and the vermis, with occlusion of the fourth ventricle, hydrocephalus with damage to the infundibular area, but no changes around the aqueduct. As a result of the study of these cases, and those of meningitis described above, this group of workers concluded that the sleep mechanism consists of a series of connected centres beginning in the infundibular region and extending caudally into the upper portion of the mesencephalon. They suggested also that damage to a portion of this series might be compensated for by the remainder of it.

Hechst [21] (1929) was to a considerable extent in agreement with this opinion, and concluded, after a careful clinico-pathological study of four cases of diencephalic tumour associated with hypersomnolence, that the medial portion of the thalamus and the gray matter around the caudal part of the third ventricle and the rostral end of the aqueduct play about equal roles in the sleep mechanism. Since the tumour in one of his cases occupied only the left thalamus, Hechst believed that hypersomnolence can result from unilateral lesions.

In his two reports of seven cases with interbrain tumour Weisz [22, 23] made one of the most important recent contributions to the study of sleep. Like Hechst and Marinesco his conclusions as to the

exact location of a central sleep mechanism were guarded. From the clinical standpoint he felt that no syndrome of the third ventricle region could be drawn up, but he was impressed by the hypersomnolence present in all of his cases. On the basis of the study of serial sections of the diencephalon in six instances, he stated that no closely localized centre for sleep can yet be postulated, although his evidence suggested that lesions in the rostral portion of the hypothalamus near the tuber cinereum were most important in the production of sleep disturbances. This author also pointed out that vascular disturbances beyond the limits of the tumour proper may be responsible for the hypersomnolence.

(3) *Experimental studies.*—The experimental production of sleep has been carried out both by stimulation and destruction of diencephalic tissue. Hess [30, 31], in 1927, using a very light electrical stimulus, was able to produce sleep in animals when he stimulated the periventricular gray matter near the massa intermedia and near the cephalic portion of the aqueduct, and the head of the caudate nucleus. He noted that the stimulation of the more ventral portion of the periventricular gray matter resulted in deeper sleep, and that the more lateral irritation resulted in sleep coming on some moments after the cessation of the stimulus.

Spiegel and Inaba [32, 33] on the other hand obtained similar results by introducing needles into the thalamus bilaterally. Puncture of the periventricular gray matter did not produce sleep in their animals.

A third method of approach to the question was used by Beattie, Brow, and Long [34]. In studying the cerebral autonomic connections these workers were able to produce sleep in cats by making a cut (1 by 4 cm.) from the anterior edge of the colliculi to the posterior edge of the pituitary fossa. These animals showed hypersomnolence after operation, as well as hypopyrexia, glycosuria, polyuria, albuminuria and contracted pupils.

In 1927 a new line of experimental attack on the problem was described by Demole [35]. He found that the injection of certain solutions, particularly calcium chloride, into the infundibular region in cats produced a characteristic sleeping state for varying periods of time. Potassium chloride had an opposite exciting effect, which could be to some degree inhibited by the later injection of the calcium salt. Similar changes, although more slowly produced, followed the intraventricular or intracisternal injections of these solutions. A number of later workers, including Cloetta and Fischer [36], LaFora [37], and Marinesco [38, 39], have confirmed the results obtained by Demole from intra-

cerebral injections. Marinesco and his group of workers summarized the results of their very extensive experimental studies as follows: (1) Puncture of the wall of the third ventricle of the cat produces a true sleep which is reversible. (2) The intracerebral injection of calcium chloride into the diencephalon favours sleep; potassium chloride injection inhibits sleep. (3) Polarization of the infundibular region, using the cathode polarization, inhibits sleep. (4) The intraventricular injection of calcium chloride results in sleep. (5) Intracerebral injection of choline, and sometimes potassium chloride, produce sleep which is preceded by agitation and muscular hyperactivity. (6) In all cases of experimental sleep in animals lesions were constantly found in the lateral walls of the third ventricle.

Keeser and Keeser [40, 41] were able to confirm in a slightly different way the theory of the importance of the action of certain chemicals upon the diencephalon in producing sleep. They succeeded in combining barbituric acid derivatives and ferric chloride and administering them to animals in large doses. The animals exhibited the usual soporific effects of the barbiturates and were then killed. Upon staining sections of the hardened brains with potassium-ferrocyanide the presence of the greater portion of the barbituric acid derivatives in the interbrain was clearly demonstrated, and suggested strongly that this was the site of action of the drug in producing sleep.

A final piece of evidence favouring a chemical or hormonal change in the sleep state was furnished by Kroll [42]. He found that acetone extracts of brains of sleeping animals produced characteristic sleep states when injected intracisternally or intravenously in cats. Whether the original sleep was produced artificially by any of the known methods or resulted sponanteously or from hibernation made no difference in the results.

To condense and clarify the data presented in this survey of the evidence related to a central sleep mechanism a brief summary is helpful. At the same time some of the difficulties involved in each method of attack on the problem may be mentioned.

(1) *Studies based on inflammatory lesions.*—Based chiefly upon cases of encephalitis, but also upon instances of embolic abscesses and meningitis, it has been suggested that the sleep mechanism is to be found: (1) in the periventricular gray matter of the third ventricle, (2) in the caudal portion of the hypothalamus and the cephalic end of the mesencephalon, (3) in the dorsal gray matter over the cephalic end of the aqueduct, (4) in the thalamus, and (5) in the region of the

infundibulum and tuber cinereum. These data are open to several comments. The lesions are in all cases widespread, and the assumption that one involved area rather than any other is responsible for the production of sleep disturbances is dangerous. The psychic changes and the general toxic effects which are present in some instances (as in cases of subacute bacterial endocarditis, or in meningitis) may considerably confuse the clinical picture. It should be noted also that in epidemic encephalitis not only does hypersomnolence occur, but inversion of the sleep rhythm, insomnia and dissociation of mental and bodily sleep (Economo). The absence of these symptoms in cases in which other lesions involve the same areas suggests that these particular sleep disturbances may be related to the character of the lesion as well as its location.

(2) *Studies based upon brain tumours.*—The many reports of brain tumour cases indicate that the sleep mechanism may be localized variously in: (1) the thalamus; (2) the hypophysis; (3) the infundibular region; (4) the caudal portion of the hypothalamus; (5) the cephalic end of the mesencephalon; (6) a chain of centres extending from the infundibular region caudally through the hypothalamus to the aqueduct. The most important failing of this body of evidence is the paucity of presentations including careful localization of the lesion. On several of the more complete reports certain other comments may be made. In considering the work of Weisz, for example, one is impressed by the large size of the lesions found. In three instances the tumour occupied the greater part of one hemisphere, and in three cases there was extensive hæmorrhage in and about the tumour. In the presence of such widespread disease one may question again the propriety of the study of only the hypothalamus on the assumption that the damage to this area is responsible for the sleep disturbances noted. In many reports the possible effects of increased intracranial pressure or very marked hydrocephalus may impair the validity of the conclusions. A striking exception is the case of Fulton and Bailey, where the clinical picture was very definite, the pathological study was complete, and the lesion was small and did not obstruct the ventricular system. This tumour occupied the infundibular region and the tuber cinereum, and encroached on the mammillary bodies.

(3) *Experimental studies.*—Curiously enough, experimental studies have led to more confusing results than the clinical reports. The evidence at hand suggests localization of a sleep-controlling area in: (1) The infundibular region; (2) the periventricular gray matter of the

third ventricle; (3) the thalamus; (4) the cephalic portion of the mesencephalon; and (5) the head of the caudate nucleus. The inconclusive nature of this work may be due in part to the difficulty of interpreting the clinical picture in animals. It is interesting to note, for example, that an attack of sleep is produced in experimental animals by a lesion or stimulus—a state of recurring hypersomnolence such as is found in humans not having been reported. It is evident, too, that to produce a lesion in any subcortical area the brain tissue intervening between this area and the surface must be to some extent injured. Marinesco has suggested that the production of large experimental lesions may cause sufficient stupor from operative shock as to obscure a brief period of somnolence.

FIG. 1.—Diagrammatic representation of the areas which are closely related to sleep disturbances, as evidenced by the studies in the literature. 1, The infundibular and tuber region; 2, the gray matter around the rostral end of the aqueduct; 3, the periventricular gray matter of the third ventricle; 4, the thalami.

Considering, then, the previously reported work relating to the localization of the sleep mechanism in the light of certain difficulties and possible sources of error, one may say that there is considerable reliable evidence favouring four areas in the diencephalon as being important in the production of hypersomnolence (fig. 1): (1) the infundibular and tuber region (supported by the cases of Fulton and Bailey, and Weisz); (2) the periventricular gray matter (supported by the experimental work of Hess and Marinesco chiefly); (3) the gray matter surrounding the cephalic portion of the aqueduct (supported by Economo's studies); and (4) the medial portion of both thalami (supported by the experiments of Spiegal and Inaba).

Materials and Methods.

The pathological studies in the three cases reported here were carried out in the following manner. Fixation was in formalin. Blocks of the tissue were cut to include the tumour and surrounding structures; these were imbedded in celloidin and cut in serial sections. Alternate fifth sections were stained by means of Weil and by hematoxylin eosin.

In any discussion of the diencephalon the variations in anatomical nomenclature tend to cause confusion. In the present report the simpler classifications of thalamic and hypothalamic structures have been given preference, in part because of the difficulty in recognizing the smaller nuclear groups without special stains, and in part because of the lack of evidence that the many minute morphological nuclei which have been described by some authors have any functional or physiological identity as units. Accordingly the terminology of LeGros Clark [43] has been used in describing the thalamic lesions and the descriptions of Malone [44, 45] are followed in referring to the hypothalamic nuclei. For reference purposes several anatomical studies of other authors (references [46 to 52] inclusive) have been included in the bibliography.

Case Reports.

Case 1 (*file number* 24813). *History.*—E. G., a 47-year-old miner, had been entirely symptom free until sixteen days before his admission. Two days previous to the onset he was struck on the head by a falling piece of coal, but noted no immediate ill effects. His first symptoms—severe headaches, blurred vision and dizziness—all coming on in attacks of several hours' duration two or three times daily, were sufficiently marked to necessitate stopping work.

Eight days prior to admission an attack of generalized tremor occurred, and on the same day mild mental changes, such as disorientation, impairment of memory and possibly visual hallucinations developed. The past history and family history revealed nothing significant.

Examination.—It was apparent that the patient was disoriented and could remember little of recent events. A generalized motor weakness and moderate ataxia of both upper and lower extremities were present. Examination of the cranial nerves showed a left external rectus palsy, bilateral choked discs and a diminution of hearing on the left. A left-sided Babinski reflex was noted.

Sleep disturbance.—On examination the patient's hypersomnolence was striking. He could be aroused by calling his name, by repeated commands, or by painful stimuli, but in the course of a few minutes would fall asleep again.

Course.—Because of the clear-cut history of antecedent trauma a chronic subdural hematoma was suspected, but when bilateral trephine openings failed

to disclose this a right temporo-parietal bone flap was reflected. No tumour was seen in this area, and the discovery that the right ventricle was very large led to the suspicion of a deep-seated, midline lesion, and the wound was closed. The patient seemed profoundly shocked, even though loss of blood had been slight and all intracranial hypertension had been relieved. He died four hours after operation.

Gross pathology.—The external appearance of the brain was normal. On sectioning the specimen, however, a moderate degree of internal hydrocephalus involving both lateral and the third ventricles was apparent. In the pineal recess lay a tumour mass measuring 2·5 by 1 cm., which extended anteriorly into the third ventricle, laterally into the thalami, and caudally to about the middle of the superior colliculi. Ventral to the lesion the roof structures of

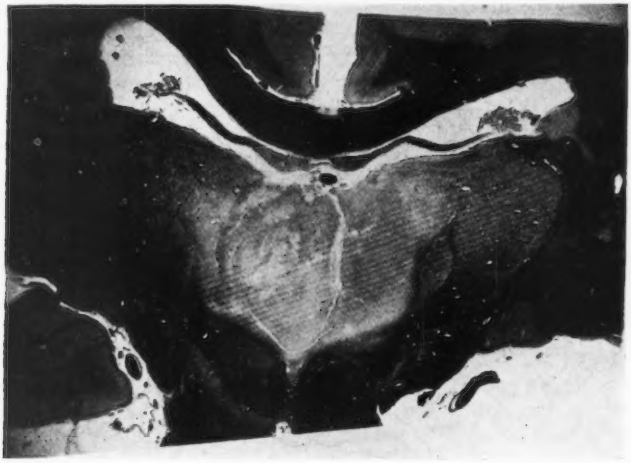

FIG. 2.—*Case* 1. The tumour is seen occupying the third ventricle, periventricular gray matter and the medial nuclei of both thalami, at the level of the caudal portion of the diencephalon. The centre-median nucleus and the external geniculate body are prominent on the right.

the anterior end of the aqueduct were compressed and invaded. The tumour appeared to be infiltrative, showed a granular cut surface, and was somewhat softer than the surrounding brain.

Microscopic pathology.—At the level of the oral end of the red nucleus the tumour could be seen projecting into the third ventricle, but not yet invading its walls. This invasion began in the immediately succeeding sections in the periventricular gray matter, the "centre median" and ventral thalamic nuclei, and the thalamic fasciculus on the right. More caudally, in sections containing the oral end of the lateral geniculate body, the lesion enlarged to occupy a portion of the right dorsomedial, "centre median," and ventral nuclei, and a thin strip of periventricular gray and "centre median" nucleus on the left. At the

level of the corpus Luysi the tumour appeared considerably larger and occupied a greater portion of the same thalamic nuclei as before. Ventrally, however, it did not invade the red nucleus or the arcuate nucleus, extending only into

FIG. 3.—Diagrams illustrating the positions of the lesions at four levels of the diencephalon in each of the three cases. A, Anterior thalamic nucleus. V, Ventral thalamic nucleus. L, Lateral thalamic nucleus. Dm, Dorso-medial nucleus. Cm, Centre median nucleus. P, Pulvinar. Lg, Lateral geniculate body.

the most dorsomedial of the fibres surrounding the red muscles. Caudal to the corpus Luysi the tumour was almost symmetrical; it obliterated the third

ventricle, spread out to occupy most of the "centre median," three-fourths of the dorsomedial, and the medial extremity of the ventral nucleus on both sides. Again the lesion remained dorsal to the red nucleus and its surrounding fibres. The fasciculus retroflexus was destroyed bilaterally at this level. In the sections caudal to this point the ventral portion of the habenula was involved on both sides as well as the medial aspect of the putamen, but otherwise there was little change in the lesion. As the tumour decreased in size it became more dorsal and disappeared soon after its invasion of the posterior commissure.

Summary of pathology.—Microscopic study showed the tumour to be a glioblastoma multiforme, filling the caudal one-third of the third ventricle and the pineal recess. The lesion began at the level of the rostral end of the red nucleus, and extended beyond the posterior commissure to invade the rostral tip of the mesencephalon. Laterally the periventricular gray matter and the thalami were infiltrated bilaterally, the dorsomedial nucleus being principally involved, with less invasion of the "centre median" and the ventral nuclei. Farther caudally the pulvinar and habenula was infiltrated and compressed on both sides. Ventrally the lesion penetrated the periventricular gray matter and reached the medial lemniscus bilaterally. The posterior commissure was infiltrated.

Case 2. *History.*—J. C., aged 50, gave a history of having been troubled first with persistent hiccoughs for one week in 1928, again for one week in October, 1931, and finally almost constantly during the three weeks preceding his admission on December 18, 1931. During the months of November and December marked mental deterioration had occurred, the patient becoming confused, apathetic and unable to remember such simple facts as his age or the names of his friends and visitors. The past history and family history revealed nothing unusual, although an attack of influenza in 1926 was noted.

Examination.—The mental failure was marked. The patient was disoriented for time, depressed, apathetic and unable to perform even the simplest arithmetic. He could not remember the name of the President or the discoverer of America. He had forgotten his age, and could not recall what he had done a few minutes before. Neurological examinations were entirely negative at first, though later a slight exaggeration of the right tendon reflexes and some ataxia of the left arm were noted. Lumbar puncture showed normal pressure and normal cerebrospinal fluid.

Sleep disturbances.—Hiccoughs and hypersomnolence were the two most striking symptoms of this patient. He slept frequently during the day even at the time of admission, and these periods of sleep became more frequent during his stay. He could be aroused readily by questions, noises or painful stimuli.

Course.—The patient was thought to be suffering with epidemic encephalitis. In spite of a variety of therapeutic measures his hiccoughs continued, his mental state and hypersomnolence grew worse, and about one month after admission he grew stuporous and died from a terminal bronchopneumonia.

Gross pathology.—In the left frontal lobe beginning at the genu of the

corpus callosum was found a tumour mass about 3 cm. in diameter, occupying chiefly the third frontal convolution, but spreading into the second frontal gyrus and the operculum. In the right side another tumour occupied the head of the caudute nucleus, causing a marked enlargement of this structure which spread out into the ventricular cavity (right lateral ventricle). It extended backward, occupying pallidum, putamen and the entire right thalamus, and infiltrating all of the internal capsule except a small portion of the genu. Laterally it spread out to involve the claustrum and compress the external capsule, insula and temporal lobe, particularly the region of the hippocampus. Medially at the level of the beginning of the iter the lesion crossed to the left side and invaded the left thalamus and gray matter around the upper end of the aqueduct. Ventrally the right corpus subthalamicum was infiltrated and the right corpus mammillare was slightly enlarged. The red nucleus and substantia nigra were not invaded. The third ventricle was compressed and apparently entirely obliterated posteriorly by the tumour, and the right anterior horn was encroached upon. Both posterior horns of the lateral ventricles were distended. The corpus callosum was slightly thinner than normal.

Microscopic pathology.—In the serial sections it was apparent that the two tumours described were connected and formed parts of one bilateral, very irregular and highly infiltrating tumour, which proved to be a glioblastoma multiforme. However, since the tumour mass on the left lay for the most part outside tho diencephalon, and was to a large extent a separate lesion, the description may be justifiably simplified by describing it briefly as a distinct neoplasm.

The left-sided tumour appeared in the serial sections, which began at the level of the anterior commissure, in the cortex and subcortical tissue of the frontal lobe and insula, and spread mesially to involve claustrum, external capsule, and the lateral border of internal capsule and putamen. Ventrally it extended through the putamen to join the tumour tissue from the opposite hemisphere. In the succeeding sections this lesion grew smaller gradually and extended farther ventally to involve a portion of the temporal lobe. Caudal to the insula the tumour was considerably diminished in size and formed a narrow subcortical strip from the internal capsule above to the temporal cortex below. Slightly caudal to the mammillary bodies the extension of the neoplasm, now a separate mass, could be seen in the globus pallidus, disappearing at the level of the red nucleus.

The diencephalic tumour mass lay principally on the right, but throughout the sections was to some extent bilateral. At the level of the anterior commissure it occupied the medial one-third of internal capsule, the entire pallidum and the ventral portion of putamen on the right. On the left the invasion was less extensive but included periventricular gray matter, globus pallidus, anterior commissure and to a slight extent the internal capsule. At a level just rostral to the chiasma the medial portion of the anterior and ventral thalamic nuclei, the ventromedial one-third of internal capsule, almost the entire globus pallidus, and the medial border of the putamen were occupied by tumour on

the right. The sublenticular area was infiltrated. Medially the tumour spread through the third ventricle (and its periventricular gray matter on both sides) to involve the medial border of the thalamus, the internal capsule, and a considerable portion of the globus pallidus on the left. Between the tuber cinereum and the mammillary bodies the right thalamus and hypothalamus were extensively damaged. The dorsomedial and anterior nuclei were slightly infiltrated, the ventromedian half of ventral and a small portion of lateral nuclei, the internal capsule, all of the hypothalamus (including n. paraventricularis, n. supraopticus, and n. tuberis lateralis), and the dorsal portion of temporal lobe were occupied by tumour on the right side at this level. The periventricular gray and most of the third ventricle were obliterated and the left dorsomedial and ventral nuclei, the medial extremity of internal capsule and

FIG. 4.—*Case* 2.—Section through the oral tip of the left red nucleus showing the tumour growing from the medial portion of the right thalamus, and involving the periventricular gray matter and the medial thalamic nuclei on the left.

the medial half of pallidum were involved. N. paraventricularis and n. supraopticus were invaded slightly but not destroyed on the left. In the sections through the mammillary bodies the tumour was somewhat smaller. The medial one-third of the right thalamus, including about this proportion of dorsomedial and ventral nuclei, was obliterated. More ventrally the periventricular gray matter, n. paraventricularis, field of Forel, zona incerta and the mammillo-thalamic tract were infiltrated. The dorsal portion of the mammillary nuclei and the n. tubero-mammillaris were invaded, but preserved relatively normal architecture. Spreading across the third ventricle the tumour involved a crescentic area about 1 to 5 mm. in width in the left ventricular wall, including the medial portion of dorsomedial and ventral nuclei, the dorso-

medial border of mammillo-thalamic tract, the periventricular gray matter, and n. paraventricularis. In sections through the rostral portion of the red nucleus the tumour was still smaller; it occupied a small portion of dorsomedial nucleus, all of " centre median " nucleus and the medial third of ventral nucleus on the right. Ventrally it invaded the field of Forel, zona incerta and the dorsal border of body of Luys, but did not involve the red nucleus. The extension across the midline lay in the periventricular gray matter, most of the " centre median " nucleus, the medial portion of dorsomedial and ventral nuclei. The tumour here lay entirely dorsal to the field of Forel. Caudal to this level the neoplasm diminished rapidly in size, lying in the dorsomedial (right) and " centre median " nuclei (bilateral), until its disappearance at the level of the external geniculate body.

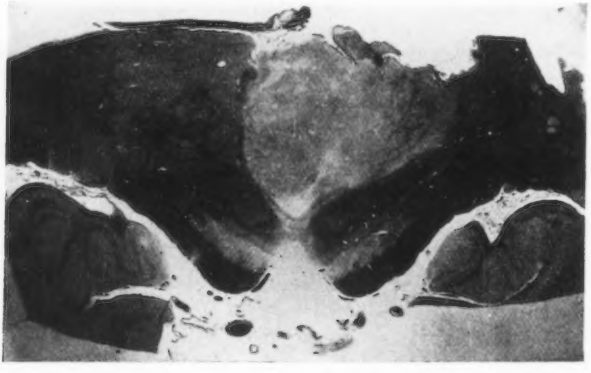

FIG. 5.—*Case* 3.—Section at the level of the oral end of the red nuclei, the tumour being seen in the medial half of the left thalamus (the section is viewed from the front so that the left thalamus is seen on the right) and filling the third ventricle almost completely. There is some compression but only very slight infiltration of the right thalamus.

Summary of pathology.—The irregularly shaped, highly infiltrating glioblastoma multiforme seen in the sections of this case consisted of two connected, roughly spindle-shaped masses of tumour. One lay superficially in the left hemisphere, extending from the second frontal convolution at the level of the genu of the corpus callosum through the insula (where it formed a band of tumour bordered dorsally by the internal capsule and ventrally by the temporal cortex) and globus pallidus, to end at the level of the red nucleus. The other, beginning chiefly in the head of the right caudate nucleus, but lying so near the midline as so involve the medial portion of both hemispheres throughout its length, extended through the medial portion of right pallidum, internal capsule, thalamus and hypothalamus to end at the level of the red nucleus and the external geniculate body. The third ventricle and medial portion of the left thalamus were involved between the same levels (figs. 2 and 4).

Case 3 (*file number* 27875).—This case is included for the purpose of control

and comparison, disturbances of sleep being entirely absent despite the presence of a diencephalic tumour. Accordingly the clinical history and details of the lesion will be omitted.

Summary of pathology.—Study of the brain in this case showed a spindle-shaped astrocytoma occupying the left diencephalon, extending from the level of the anterior columns of the fornix to the rostral portion of mesencephalon. Beginning in the wall of the left lateral ventricle the tumour lay chiefly in the third ventricle and dorsomedial part of the left thalamus, including anterior, ventral, dorsomedial, " centre median," and a portion of lateral nucleus, the ventromedial part of pulvinar and the habenula. It crossed the ventricle to invade periventricular gray matter and at some levels a narrow strip of dorso-medial and " centre median " nuclei of the right thalamus. The left mammillo-thalamic tract, left fasciculus retroflexus and the posterior commissure were interrupted by tumour. At no point was the hypothalamus invaded (figs. 2 and 5).

Discussion.

(1) *Summary of cases.*—It is apparent from the microscopical study of the serial sections of Cases 1 and 2, that the areas involved in both instances consist essentially of (1) the periventricular gray system and the small medially-placed nuclei; (2) the dorsomedial nucleus; and (3) the " centre median " nucleus on both sides of the mid-line. The actual boundaries of the tumours, of course, did not coincide exactly with nuclear limits, but the portions of anterior and ventral nuclei and pulvinar which were bilaterally involved in both cases were so small that they may justifiably be omitted from the discussion. Furthermore, bilateral injury to the pulvinar occurred in the control case without the symptom of hypersomnolence.

It is important and interesting to note that the hypothalamus was to a considerable extent uninjured in the first two cases. The nucleus paraventricularis was involved in both, and the rostral portion of the n. supraopticus, the n. tuberis lateralis, and the dorsal part of the mammillary and tubero-mammillary nuclei were destroyed unilaterally in Case 2. Finally, the termination of the tumour within the diencephalon in the cases with hypersomnolence as compared to its extension into the midbrain in Case 3 deserves mention.

(2) *The problem of a sleep centre.*—As Troemner [2] has pointed out the three great questions concerning sleep are (1) the nature of sleep; (2) the question of the existence of a sleep centre; and (3) the location of such a centre if it exists. Leaving aside the other two questions for a moment the possibilities of the existence of an area in the central nervous system controlling the sleep rhythm may be considered. At

first glance the association of hypersomnolence with a relatively small diencephalic or mesencephalic lesion would seem to be strong evidence for such a centre. There are several arguments against such a conclution, however. First, the entire theory of extreme localization of cerebral function has been to some extent unsettled by recent work. Secondly, there is still no conclusive proof of the existence of strictly localized centres in the diencephalon for other processes which are at least approximately comparable to sleep—vascular control, respiratory control, water metabolism, or temperature control. While general areas which are apparently essential to the maintenance of these functions are known, the assignment of any one function to a particular nuclear mass is not supported by the evidence at hand. Finally, and not the least in importance, there remains the fact that postulation of a sleep centre in any one small area leaves unexplained the hypersomnolence associated with lesions in other positions.

(3) *Structure and connections of the areas involved in the reported cases.*—If no sleep or waking centre may be postulated, what explanation can be offered to explain the clinical and experimental data dealing with the problem? In an attempt to attack this question from another angle the physiology and anatomy of the areas involved in Cases 1 and 2 may be reviewed. These areas it will be remembered were principally (i) the periventricular system and the centrally placed nuclei; (ii) the "centre median" nucleus; and (iii) the dorsomedial nucleus.

(i) *The periventricular system.* Clark [43] presents concisely the phylogenetic knowledge of this structure. "In all vertebrates, the dorsal part of the diencephalon and the hypothalamus are linked together by a strand of cells and fibres which form what may be called the periventricular system. In the cyclostome brain this primitive connecting link is apparent as a narrow band lying vertically in the lateral wall of the third ventricle and connecting the habenula with the hypothalamus. Through this periventricular system the somatic correlation centres of the diencephalon are brought into functional relation with the visceral correlation centres." Similarly Rioch [53] noted in the cat and dog that the fibres of the periventricular system connect the nuclei of the medial preoptic areas and hypothalmus with the nuclei of the medial thalamic group, and Huber and Crosby [54] arrived at the same conclusion.

The mid-line nuclei, while probably playing a less important role in man, have been shown definitely in many lower forms (Gurdjian [55], Vogt [56], Clark [43], Rioch [53]) to function not only as commissural nuclei, but in connecting the dorsal and central thalamic centres through the periventricular system.

(ii) *The centre median nucleus.* On the basis of comparative anatomical studies Clark believed the "centre median" nucleus functions as a connecting and correlating mechanism for other thalamic elements. Rioch [57] has presented evidence of a similar character which suggests that this nucleus represents the elaboration of an interstitial group of cells and belongs neither to the medial nor to the ventral group in a strict sense. Finally, Clark and Boggon [58] have shown experimentally (by degeneration studies) that the "centre median" nucleus is connected by short tracts with the surrounding thalamic nuclei and the periventricular system.

(iii) *The dorsomedial nucleus.* It seems possible that this nucleu is not present, or at least not important, in submammalian forms, and Clark has pointed out that its development in the mammals parallels the increasing size and complexity of the forebrain. This is quite in keeping with the good evidence which he has presented that the dorsomedial nucleus is closely connected with the frontal cortex by both afferent and efferent fibres. It is also known to be linked with the other thalamic nuclei, with the striate body, and particularly with the periventricular gray system.

Conclusions regarding the localization of the sleep mechanism. From this brief review of the structure and connections of the dorsomedial and "centre median" nuclei and the periventricular system it is safe to assume that these structures serve as important correlating mechanisms and connecting links between the cortex and thalamus on the one hand and hypothalamus on the other. Furthermore, it has been shown by Beattie, Brow and Long [34, 59, 60] that there are doubtless connections between the hypothalamus and mesencephalon and possibly pons and medulla.

When we consider then the present anatomical and physiological knowledge of the areas involved in the cases showing hypersomnolence which were studied, and the accumulated evidence of other similar studies, it seems probable that the sleep-rhythm is controlled by a relatively wide area (perhaps located in the medial portion of the thalamus) acting as a correlating centre for many cortical, endocrine and exogenous stimuli, and closely bound up with a cortico-thalamico-periventricular-hypothalamico-mesencephalic chain. Since the lesions which have been known to be associated with hypersomnolence have all been located somewhere in this chain of closely connected structures it seems reasonable to believe that the interruption of afferent or efferent impulses to such a central mechanism may also cause disturbance of

sleep. From our present conception of its structure it is much easier to regard the gray matter surrounding the third ventricle, or about the rostral end of the aqueduct, for example, as transmitting important afferent or efferent impulses concerned with sleep, than as a static centre controlling such a complex function. The direction of the nerve impulses in such a chain, its relation to the central part of the autonomic system, why its interruption should seem to cause hyposomnolence, rather than insomnia, whether its destruction cuts off inhibitory or stimulatory impulses, whether this chain represents part of only one of two balanced mechanisms: all these remain problems for future solution. For the present, however, the conception of the central control of the sleep-wake rhythm as a rather diffuse correlation mechanism which is dependent for its normal function upon the integrity of a thalamico-periventricular-hypothalamico-mesencephalic chain of neurones, seems best to explain our clinical, experimental and physiological data.

There remains the consideration of Case 3. Here the lesion involved all of the areas destroyed in the first two cases, but almost entirely unilaterally. While the tumour did fill most of the third ventricle and invaded the periventricular gray matter and medial portion of the opposite side in places, it penetrated to a depth of only 1 to 2 mm., except in its caudal extremity which damaged the right pulvinar slightly more extensively. In a careful comparison with the other cases the most logical explanation of the absence of hypersomnolence in this instance seems to be the unilateral position of the tumour.

The evidence relating to this point is somewhat conflicting. Almost all of the carefully studied cases of tumour associated with hypersomnolence produced bilateral disturbances. Spiegel and Inaba could produce hypersomnolence in animals only by bilateral thalamic lesions. On the other hand, Hechst has reported the occurrence of excessive sleep in a patient who was found at autopsy to have a tumour involving only one side of the diencephalon. There is as yet no available explanation of this contradiction, but in the cases of this series bilaterality seemed a prerequisite to the production of hypersomnolence.

Summary.

(1) A survey of the literature dealing with lesions of the interbrain associated with hypersomnolence shows: (i) The evidence favouring various localizations of the sleep mechanism in the diencephalon is inconclusive and not entirely satisfactory. (ii) The relatively small number of careful clinico-pathological and experimental studies suggest

that hypersomnolence may be caused by lesions in : (*a*) the infundibular region ; (*b*) the periventricular gray matter ; (*c*) the region about the cephalic end of the aqueduct ; (*d*) the thalamus (if involved laterally).

(2) A careful clinico-pathological study of three cases of relatively small tumour of the diencephalon, two associated with marked hypersomnolence, and one showing no sleep disturbance, suggests that in these cases bilateral damage to (1) the dorsomedial nucleus of the thalamus, (2) the " centre median " thalamic nucleus, and (3) the periventricular system and mid-line nuclei, was responsible for the alteration of the sleep rhythm.

(3) On the basis of the cases studied, the present anatomical and physiological knowledge of the diencephalon and the accumulated evidence in the literature, it is suggested that disturbances of sleep result from lesions of a rather diffuse central correlating mechanism, which may lie in the medial thalamic nuclei, or from the interruption of a thalamico-periventricular-hypothalamico-mesencephalic chain of neurones conducting impulses to or from such a mechanism.

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THE CEREBRAL BLOOD FLOW DURING SLEEP IN MAN.[1]

BY F. A. GIBBS, E. L. GIBBS AND W. G. LENNOX.

THAT sleep is produced by changes in cerebral blood flow is a theory which in past years has had wide support. Mosso [1], in 1881, believed there was cerebral anæmia during sleep because of observations made with a tambour placed over the skull defect of a patient. The anæmic theory of sleep has been supported by various physiologists, including Leonard Hill, who wrote "there can be no doubt that sleep or lethargy is associated with cerebral anæmia" [2]. Others have believed that sleep was caused by cerebral congestion. One of the latest contributions is that of Stevenson, Christensen and Wortis [3]. These authors observed increase in intracranial pressure (registered by means of a tambour placed over a defect in the skull) which they interpreted as evidence of fatigue of the sympathetic centre controlling the tone of cerebral vessels. This resulted, they suggested, in dilatation of the cerebral vessels, giving the increase in pressure and a pulling apart of the neurons with interruption of nervous activity.

Although the theory of a vascular explanation of sleep is not emphasized to-day, it is still listed as a possible cause [4] and no direct evidence has been brought forward to disprove it. This, of course, is because observations of cerebral blood flow in man have been indirect, deductions being drawn from changes in intracranial pressure or changes in systemic blood-pressure or in the blood-flow elsewhere in the body. By means of a method recently devised we have found it possible to obtain direct evidence of cerebral blood-flow with reference to sleep.

Records were made of the changes occurring in the blood-flow through an internal jugular vein of anæsthetized patients. The instrument used was a needle flow recorder of a type which one of us has previously described [5]. It consists essentially of a stilet with an electrically heated tip. This stilet is inserted through a hollow needle

[1] From the Neurological Unit of the Boston City Hospital, Boston, Mass. This study was aided by a grant from the Josiah Macy, Jr., Foundation. This paper is No. 37 in a series from the Department of Neurology of Harvard Medical School entitled, "The Cerebral Circulation."

into the lumen of an internal jugular vein. A constant electric current is applied to the tip of the stilet sufficient to heat it to a temperature slightly higher than that of the blood. As the blood flows past the heated tip it is cooled. When the blood flows more rapidly the tip becomes cooler, and when the blood flows more slowly the tip becomes warmer. The temperature of the tip is measured by means of thermo-junctions in series with a galvanometer. In order that a change in body temperature should not be misinterpreted as a change in flow, the cold junction is mounted on the stilet behind the hot junction; it then becomes possible to measure not the absolute temperature of the tip, but the difference in temperature between the heated tip and the body of the stilet. This difference in temperature varies only slightly with changes in body temperature, but greatly with changes in blood-flow.

The instrument records changes in the velocity of the surrounding stream. If the cross section area of the stream remains constant, changes in velocity may be interpreted as changes in volume flow. We punctured the internal jugular vein close to its point of exit from the skull, a situation where fluctuations in calibre would not be expected to occur, for where the vessel pierces the skull it has an essentially rigid wall. We believe, therefore, that any observed changes in velocity can be interpreted as changes in volume flow, and where no such changes occurred the volume flow remained constant.

In our experiments the patient lay quietly on a table. Records of the blood-flow and of respiration were taken continuously for a period of from one to two hours. In four instances records were obtained covering periods in which the subjects (epileptic patients who had no disorder of sleep) went to sleep. In no case was there evidence of a significant change in cerebral blood flow either when the patient fell asleep or when he awoke. During calm sleep the cerebral blood flow tended to fall gradually, but this seemed related to a decrease in restlessness and not to sleep *per se*.

A typical record is shown in fig. 1. The changes in blood flow which did occur were probably passive responses to changes in systemic arterial pressure. Certainly, the period of sleep was not accompanied by greater fluctuations in flow than occurred in the control-waking periods.

One of the patients studied had narcolepsy and a history of cataplectic attacks. The record shown in fig. 2 was obtained during one of his characteristic sleep attacks. The general level of the cerebral blood-flow was not influenced by the occurrence of this period of sleep.

These observations indicate that the impairment of consciousness

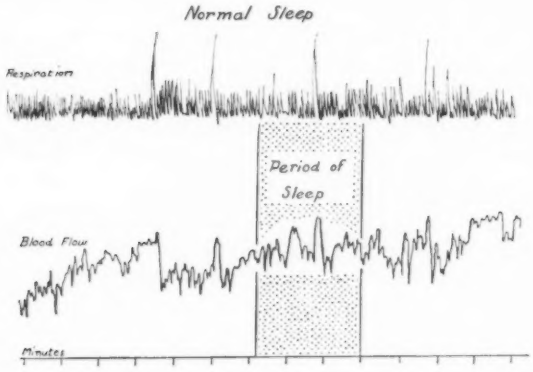

FIG. 1.—The cerebral blood flow during normal sleep. The tracing at the top represents respiratory movements of the chest; the one in the middle, alterations in blood flow in an internal jugular vein; the line at the bottom shows time in minutes. The approximate period of sleep is shown by the dotted area. In this record, the full sensitivity of the string flow recorder was being utilized and minor fluctuations in flow give the record its somewhat toothed appearance.

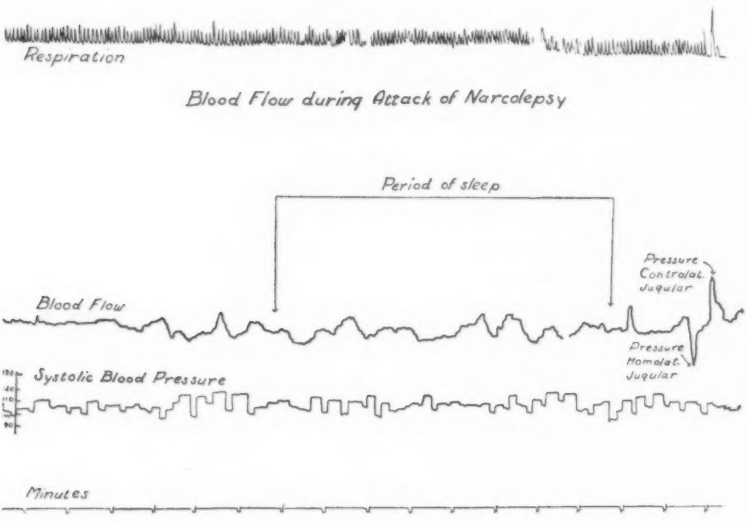

FIG. 2.—The blood flow during a period of sleep in a patient with narcolepsy. Tracings as in fig. 1 except that brachial blood pressure is recorded below the record of the blood flow. At the end of the period of observation the apparatus was tested by light pressure applied over the homolateral jugular vein below the needle (marked Pressure Homolat. Jugular) and then over the contralateral jugular vein (marked Pressure Contralat. Jugular).

which occurs in sleep is not due to a change in the total cerebral blood flow. We found this to be true also in regard to various other types of unconsciousness, notably in petit mal seizures [6] and in syncope from carotid sinus stimulation when no fall in blood-pressure occurred [7] On the other hand, unconsciousness which is associated with orthostatic syncope or with carotid sinus stimulation in which there is a preliminary fall of blood-pressure, is preceded by a sudden and pronounced decrease in cerebral blood flow as measured both by the blood flow recorder and by analysis of the oxygen content of blood from the internal jugular vein [7]. That the flow in itself is not the determining factor is shown by the fact that pronounced diminution of flow can be produced by such procedures as quick change in posture or hyperpnœa [8] without inducing sleep or alteration of consciousness. In unconsciousness produced by the breathing of nitrogen, the cerebral blood flow is increased [8].

A vasoconstriction in a small area of the brain would not have been detected by our instrument. It is possible that circulatory changes, confined to some small portion of the brain principally concerned with sleep, might induce sleep. That the " sleep centre " should be activated by a localized vasoconstriction would appear, however, to be a somewhat elaborate hypothesis for which there is, at present, no direct evidence.

The older observations by means of a tambour deserve some explanation. By the more exact means of observing the pressure of the cerebrospinal fluid, we have confirmed the tambour observations of Stevenson and others that an increase in intracranial pressure takes place when the subject is falling asleep. This increase is, however, slight, amounting to only 20 or 30 mm. of spinal fluid. Probably this increase is not due to an exhaustion of cerebral vasomotor nerve centres but to an increase in venous pressure, or else to a decrease in the respiratory movements and a consequent slight accumulation of carbon dioxide in the blood which enlarges the vascular bed, without overbalancing a coincident slight fall in blood-pressure, and without altering the cerebral blood flow.

Available information does not yet suffice to explain the mechanism of sleep, but the work of Pavlov with conditioned reflexes and internal inhibitions and that of Hess with stimulation experiments suggest that the mechanism is an essentially nervous one. In any case, we feel that the data presented here should form a *requiescat in pace* for a vascular theory that has too long haunted textbooks and neurological literature.

Conclusion.

Observations of the cerebral blood flow in man have been made by means of a thermo-electric blood flow recorder inserted into an internal jugular vein. The onset and termination of sleep in subjects without sleep disorder and in one patient with narcolepsy were not accompanied by a significant change in the flow of blood through the brain.

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ON THE "SYNDROME OF THE PREMOTOR CORTEX" (FULTON) AND THE DEFINITION OF THE TERMS "PREMOTOR" AND "MOTOR": WITH A CONSIDERATION OF JACKSON'S VIEWS ON THE CORTICAL REPRESENTATION OF MOVEMENTS.

BY F. M. R. WALSHE.

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I.—Introduction.

A development of recent clinical and experimental studies of the "grasping" phenomena seen in association with certain lesions of the frontal lobes is the formulation by Fulton and his collaborators [10, 13, 19, 20] of a "syndrome of the premotor cortex."

They believe that both in man and in apes a characteristic group of motor disorders meriting this title is to be observed.

The evidence submitted in support of this hypothesis is mainly experimental, and consists in observations made upon apes after circumscribed cortical ablations, but it has recently been supplemented by a clinical case of glioma of the frontal lobe which, they believe, confirms the conclusions reached from experiment and warrants their application to man.

In considering the investigations which have led to the description of this syndrome, it is essential to understand the nomenclature employed by the authors. By the term "motor area" they understand that part of the precentral convolution adjacent to the fissure of Rolando in which are found the giant cells of Betz. This corresponds approximately with Campbell's "precentral area," with Brodmann's "area 4," or with Economo's "area giganto-pyramidalis F A γ" [3, 7, 9].

The "premotor area" lies immediately anterior to the above. It corresponds with Campbell's "intermediate precentral area," with Brodmann's "area 6," and with Economo's "area frontalis agranularis, F B," together with the anterior and ventral part of his area F A.

Now it must be emphasized that the term "motor" or "excitable" cortex is based upon physiological grounds, and denotes the possession by the region so named of certain physiological properties. It implies nothing of the cellular structure of the region in question. This has been generally understood both by histologists and by experimental physiologists.

Thus Brodmann [3] says that his areas 4 and 6 together correspond with the motor cortex. Economo expresses a similar view, and it has been only by Campbell [7] that any suggestion has been made that his precentral area is co-terminous with the motor cortex properly so-called.

But in the papers we are to consider this view of Campbell's has been adopted, and in describing the two areas in question histological and physiological terms have been used as though interchangeable, though it is nowhere explicitly stated that any departure from the customary sense of the term "motor cortex" has been made. Considerable confusion has been created thereby, but for our present purposes we will use the words "motor" and "premotor" in the senses employed by Fulton and his collaborators, considering finally the influence this usage has upon the evaluation of their conclusions.

As Fulton [12] points out, the notion that the region immediately anterior to the motor cortex may have important functions in the synthesis of voluntary movements is no new one. Jackson placed his "highest level" of cortical function in the "præfrontal region," and it was perhaps natural for Campbell, as a histologist, to wish to give it "a local habitation and a name" in the intermediate precentral area he had delimited. Campbell [7] further drew attention to the origin of the fronto-pontine tract in this region and suggested that the latter and the cortical region from which it took origin might represent part of

Jackson's "highest level," the precentral area corresponding to the "middle level." But, as we shall see, so complete an identification of a cyto-architectonic field with a physiological entity is not justified either on histological or upon physiological grounds.

In 1909, Bergmark [1] pointed out that occasionally hemiparesis of cortical origin is unaccompanied by spasticity—unlike the common hemiplegia of capsular origin, while in 1919 the present writer [24] drew attention to various clinical and experimental observations which raised the question as to whether the spasticity accompanying some cerebral paralyses might not possibly be a consequence of a negative lesion of a second descending pathway; namely, the fronto-pontine tract, but no conclusions were drawn.

Again, the idea of "eupraxic centres" lying anterior to the true motor cortex is an old one, such a centre being one wherein "movements are combined ideationally, to be innervated in the sensomotorium (Wilson [26])." It finds a lucid exposition very relevant to our present subject in Wilson's paper published in this Journal: "A Contribution to the Study of Apraxia."

More recent studies of the "grasping phenomena" have again brought to the fore this question of the rôle of the frontal lobe in movement and in posture, and the series of papers by Fulton and his collaborators, to be considered, represents an attempt to throw light upon it.

It is the purpose of the present paper to review the findings and conclusions of these observers, and to consider the probable nature of the cortical representation of movements. We shall also have to consider what may properly be understood by the term "motor cortex."

But before we begin, a little retrospect may be permitted. The past quarter of a century has seen the identification of a number of newly isolated syndromes correlated, on evidence of variable quality, with local lesions in regions of the brain previously little considered by clinical neurologists. Almost invariably we find that, interest once aroused in some particular region of the brain in this way, syndromes localized in it have freely multiplied and functions have been lavishly showered upon it. The corpus striatum and, more recently, the hypothalamus provide cases in point. Outside the neuraxis the sympathetic system also affords an example of the kind.

Frequently much of this new work fails to stand the test of time and the labours of the student in assessing it all are considerable.

The lesson should be of value to us, and in approaching a region of the brain now becoming a focus of attention, namely, the "premotor"

region of the cerebral cortex, we shall do well to be cautious in accepting new attributions to it—either of symptoms or of functions—more especially if this should involve removing them from regions their association with which has been firmly established by earlier work.

II.—The Clinico-Pathological Evidence for the so-called Premotor Syndrome of Fulton in Man.

The direct evidence submitted by Fulton and his co-workers consists so far in but a single case [20]. The lesion was a glioma of the frontal lobe, and hence the syndrome developed gradually—the component signs appearing in what they believe to be a characteristic and pathognomonic sequence. These signs, in order of their appearance, are as follows: (i) Gradually increasing awkwardness in an extremity, affecting more particularly highly integrated digital movements, such as those involved in sewing, piano playing, buttoning a shirt, and without impairment of gross movements; (ii) early appearance of spasticity and increase of tendon-jerks; (iii) "forced grasping"; (iv) late appearance of weakness of grasp and of other "gross movements"; and (v) vasomotor disturbances of the affected parts.

Jacksonian attacks may or may not appear, and the authors believe that a careful examination of the sequence of events will allow of the recognition of the premotor syndrome even before the development of "forced grasping."

They do not record any special clinical studies of a syndrome of the true motor cortex, but they believe that when this develops progressively its signs will be as follows: (i) Generalized "weakness" of the extremity, especially of the grasp, appears precociously; (ii) spasticity if present at all appears late; and (iii) there is no forced grasping. Acute lesions of this region, on the other hand, produce flaccid paralysis and depression of reflexes.

The attribution of the first of the two syndromes summarized above to an exclusively premotor lesion is not one that can be readily accepted as it stands, for in respect of all but its third component, namely, "forced grasping," it represents a sequence of events and signs common to every case of progressive hemiplegia. In particular, the initial loss of isolated and skilled movements of the fingers, and—with the deepening of this loss—the spread of impairment of movement to include larger and simpler movements and those of the proximal segments of the limb, illustrate that "compound order of dissolution" described by Jackson [17] as so characteristic of hemiplegia as ordinarily seen in man. Nor is this

transfer of hemiplegia from lesions of the motor area and the pyramidal system to lesions involving only the premotor area and an "extra-pyramidal motor system," rendered more convincing by the summary given of the syndrome of the true motor cortex and the pyramidal system. This does not call up in the clinical observer's mind anything with which he is familiar. We are told that characteristic of this syndrome is not loss of skilled movements of the fingers, but rather a "generalized weakness" of the limb; a loss of power rather than a loss of purposive movements. Since this conception of "weakness" as typical of motor area and pyramidal lesions is strongly emphasized by Fulton and his collaborators and placed in contrast to loss of purposive movements, it must be submitted to some examination.

It seems that we have here a false antithesis between "weakness" on the one hand, and impairment or loss of movements on the other. For example, we find (Jacobsen [18]) that after a motor cortex ablation the affected limb is said to have recovered "motor power," although some hand and finger movements are permanently lost. No such distinction between "power" and "movements" can be drawn. A limb can do nought else than move, and the expression "loss of power" can have no other meaning than "loss of movements."

Further, in descriptions (Fulton and Viets [13]) of the "weakness" associated with motor cortex lesions, we read of paralysis of "muscles" or of a "a specific muscle group" as though muscles and not movements were represented in the cortex. Indeed, it is clear that this is the category in which the writers are thinking, though no sound hypothesis of cortical motor functions can be built upon such a basis. This antithesis between "weakness" and "loss of movements" has no foundation in reality, but seems forced upon the writers by the exigencies of an hypothesis which requires that there shall be two kinds of hemiplegia, "motor" and "premotor." As to the nature of the paralyses following cerebral lesions, Jackson expressed the facts clearly as follows: "I would point out that loss of some movements of the whole of a part, with persistence of some other movements of the whole of that part, is an exceedingly common thing. Take the case of an imperfect paralysis of an arm in ordinary hemiplegia, or after an epileptiform seizure. To say that the arm is 'weak' is misleading. The patient has lost some movements of the whole of the limb, and yet retains other movements of the whole of the limb. Often enough there is loss of some of the most 'delicate' movements, with, at the same time, the retention of many 'coarser' movements. Unable to button his shirt,

the patient may be able to grasp strongly, or to strike a heavy blow" [17].

Of the innumerable different movements of which the human hand and arm are capable, some are relatively simple and both early and easily learned. Others are more complex, especially those employing the digits, and much practice goes to their perfecting. Such distinction as we may wish to make between these two extremes is best expressed by Jackson's antithesis, "automatic" and "voluntary," or "general" and "special" respectively. But these are distinctions of degree and not of kind, and in drawing them we are neither required to, nor justified in, postulating qualitatively or topographically distinct cortical representations for the two extremes.

There are *many degrees* of hemiplegia, but only *one kind*, and the expression "loss of power," or "paralysis of muscles," is not applicable to it.

Nor may we invoke the appearance of spasticity as a sign necessarily differentiating the premotor syndrome (if there be one) from the motor syndrome, since the rate of development of the lesion, and its progressive or stationary character, are factors which enter largely into the matter.

In this case, therefore, the "forced grasping" is the only component sign of the syndrome which may be confidently ascribed to involvement of the premotor region. The hemiplegia must be assumed to be a consequence of interference with the functions of the motor cortex and its projection system, of which it is a typical example, unless it can be proved that the lesion was in fact wholly confined to the premotor region and was incapable of provoking "neighbourhood symptoms" in the contiguous motor region.

This cannot be proved, for the lesion was a cystic astrocytoma which "pointed" in the frontal cortex just anterior to the ascending frontal convolution. As is well known, it is quite impossible with the naked eye, or in the absence of a minute histological examination of the hemisphere, to determine the limits of an infiltrating growth of this nature. Its margins are invisible, and its extent always greater than can be seen macroscopically. The mass removed at operation was 22 c.c. in bulk, and we may not assume that it comprehended the entire tumour substance. We cannot know to what degree the motor cortex was infiltrated by growth, or its functions disturbed by œdema or reactionary changes. In short, the case does not provide material from which Fulton's deductions can be drawn.[1]

[1] Twenty-five years ago, Horsley [16] reported the results of an isolated ablation of the arm area of the motor cortex in the human subject. Referring in his paper to other cases on record

In his most recent paper [10], Fulton uses the term "tonic innervation" as a synonym for "syndrome of the premotor cortex," and states that forced grasping never occurs as an isolated symptom, but always associated with the other components of the syndrome enumerated above. It is not possible to accept these statements. Tonic innervation, a term first employed by Wilson and Walshe [27], was used to designate tonic grasping and this alone, and it was never associated by these writers with the hemiparesis which accompanied it in the cases recorded in their paper. Subsequently, Walshe and Robertson [25] have used the term as applying only to the proprioceptive tonic grasping reflex, isolated by them from the complex phenomenon now generally known as "forced grasping." This reflex reaction does occur from time to time in man in the absence of any paresis, change in the tendon jerks or spasticity; that is, without any of the other components of Fulton's syndrome, and one such case is reported by Walshe and Robertson in the paper referred to, and others have since come under the observation of the present writer. There can, therefore, be no justification whatever for using the term "tonic innervation" as synonymous with Fulton's "syndrome of the premotor cortex." To do so is to plunge the nomenclature into unnecessary confusion, and, in so far as reflex proprioceptive grasping may occur without the other components of this syndrome, it is, of course, inaccurate.

In the case of the human subject, therefore, the evidence adduced does not support the occurrence of such a syndrome of the premotor cortex as has been described by Fulton and his collaborators. This is not to say that there are no motor syndromes characteristic of lesions in the frontal lobe anterior to the true motor cortex. What evidence there may be for frontal motor syndromes will be considered subsequently.

III.—The Experimental Differentiation of "Premotor" and "Motor" Syndromes.

It is indisputable that in this matter the experimentalist can command opportunities denied to the clinical observer, but the latter retains the advantage of observing human material and has not to draw inferences from ape to man. Again, it is only rarely (as in Horsley's case of cortical ablation [16]) that a therapeutic intervention in man

from which conclusions had been drawn as to the functions of this region of the cortex, he wrote:—"With the utmost respect for the opinion of the many distinguished writers on this subject who have published instances of lesions in this region, I venture to object to evidence derived from cases of extensive tumour as scientifically not valid for this purpose."

fulfils the conditions of a planned animal experiment. The manner of development of a disease process in man differs, also, from that of the experimental lesion. In other words, in comparing experimental lesions in animals with the lesions of disease in man, we see that neither the material nor the event is quite the same. In this way the drawing of valid inferences is sometimes rendered difficult.

The series of experiments we are to consider illustrates these points in many ways. Thus, the sequence of cortical ablations in some of the combined motor and premotor experiments was carried out so rapidly that the motor state of an affected limb had not reached equilibrium before it was further modified by the supervention of a second lesion in another cortical region. Thus, however precise the lesions, the apportionment of the final motor state between them has something of a speculative character. Again, ablations of the premotor cortex are carried out on the very threshold of the contiguous precentral cortex, and it would be contrary to experience if transient "neighbourhood symptoms" were not produced to complicate the picture. It is essential, therefore, to differentiate carefully between immediate and transient disorders of function, and later developing and more persisting disorders. That such transient "neighbourhood symptoms" ensue after surgical interventions involving the cerebral hemisphere in man is a commonplace, and even in these experimental procedures they are found to occur. Thus Fulton and Kennard ([12], experiment 7, p. 193) found a transient paresis of an arm after ablation of the leg area of the motor cortex.

Again, it is somewhat hazardous to compare the "immediate" spasticity of brief duration that may follow an ablation of the premotor cortex with the more gradually developing residual spasticity of hemiplegia in the human subject.

Although there is nothing in these considerations not perfectly familar to the clinical neurologist who is constantly seeing them exemplified, yet it may be useful to recall their importance to him when he comes to assess the bearing of experimental lesions of the brain upon the elucidation of the symptoms of lesions in man.

Fulton and his collaborators summarize their observations and draw their conclusions as follows: (i) Lesions restricted to *the motor area* give rise to flaccid paralysis. The return of "motor power" and of normal posture is complete except for the "muscles" of the digits. In the chimpanzee a Babinski plantar response ensues. Spasticity never occurs. (ii) Lesions restricted to *the premotor area* produce as their primary

symptom a disturbance of skilled, acquired movements. Animals trained to carry out special movements of this order suffer impairment of "the capacity to execute" them. On the other hand, "gross power" is not affected and grasp remains good even when fine movements are impaired. Spasticity and increase of tendon-jerks and "forced grasping" are also present. Some vasomotor changes may appear in the affected limbs. From these observations the following conclusions are reached: (i) The premotor area is the chief cortical representation of the extrapyramidal motor system and subserves "the integration of complex volitional movements and postural adjustments." (ii) Within certain limits (nowhere defined) the pyramidal system is able to compensate for loss of the premotor cortex, and, in its turn, the premotor system is able to mediate certain voluntary movements in the absence of the pyramidal system.

It is noteworthy that these conclusions contain no statement as to the functions now assigned to the motor cortex and pyramidal system, since, as we shall see, those attributed to them by Leyton and Sherrington are boldly transferred to the premotor cortex and an extrapyramidal system.

Our task of assessing the experimental evidence in favour of the occurrence of two distinct syndromes, motor and premotor, would be simple could we assume that the summary just given adequately generalized the facts of observation as recorded by Fulton and his collaborators in their protocols, or justified their conclusions. But we cannot do so, for a study of these protocols reveals wide divergences on essential points between observation and summary thereof. We must, therefore, make our own analysis of the facts and draw our own conclusions, and in doing this it will be of value to describe—as standards of comparison—the results of motor cortex ablation in man as reported by Horsley, and in the chimpanzee as reported by Leyton and Sherrington [22].

(i) *Ablation of the True Motor Cortex in Man and Apes.*

The human subject (Horsley [16]).—The patient was a youth who suffered from violent athetotic movements of the right arm. When the limb was quiet his movements are described as being normal and powerful. The reflexes were normal. The arm area of the motor cortex was carefully delimited by stimulation in the usual way, and it was then carefully excised with minimal disturbance to the blood-vessels. The excised gyrus was examined histologically by Holmes and identified as

of true motor cortex structure. The immediate results were disappearance of athetosis and total loss of voluntary power in the limb (right arm). During the ensuing weeks the return of voluntary power followed the usual course. At the end of the third week abduction and adduction of the shoulder; next, flexion of the elbow, then extension of the elbow and flexion of the wrist. Digital movements returned later; first, flexion of the thumb, then extension of this and the other digits, the little finger moving not at all. Horsley then observes that "As regards flexion, the complication of hypertonia comes in, because the ordinary hypertonia or contracture affects as usual the most paralysed part, and therefore when the digits are flexed the small fingers curl up into the palm, and the wrist, instead of remaining extended, follows suit." Finally, the hypertonia was most marked in the flexors of the ulnar fingers and remained as a permanent residual state. Fine, isolated movements of the digits never returned. With the sensory defects noted we are not here concerned.

Fortunately for our present purpose this case was the subject of intensive investigation by Head and Holmes during the course of their studies on "Sensory Disturbances from Cerebral Lesions" (this journal, 1911, 34, 102), and their notes record that seven months after the cortical ablation there was "distinct increase of tone in all muscles from the elbow distally. The fore-arm cannot be supinated without the exertion of force continuously applied." Similarly, force was required to bring the fingers and hand into the same line as the forearm. On relaxing this force the hand and fingers slowly went back into flexion again. The left arm jerks were brisker than the right.

At the elbow there was fair power of voluntary flexion but less of extension. Supination was weak and incomplete, pronation stronger and more complete. Flexion of the third and fourth fingers was complete in range, but that of the index very incomplete and feeble. The two radial fingers could be almost fully extended, but the remaining fingers very feebly and incompletely. There was no power of flexion of the thumb, but feeble extension.

Associated movements (symmetrical) were present in the left hand on forceful movements of the right.

There was slight general wasting of the limb.[1]

Leyton and Sherrington's findings on isolated ablation of the arm area *in the chimpanzee* are identical with those recorded above as

[1] The writer is indebted to the courtesy of Sir Henry Head and Dr. Holmes for the opportunity of studying their notes of this case.

occurring in the human subject. Thus, the immediate result was loss of movements in the limb, maximal for those of the digits and minimal for those of the proximal segments of the limb. The lost and impaired movements of the latter rapidly returned, but the purposive movement of the digits, particularly isolated movements of thumb and index, were at once the most severely impaired and the most imperfectly restored. The original scar was then re-excised at a second operation. At this juncture these observers note that "the tendency to contracture noted before the second operation has become more pronounced. The arm tends to be kept partially flexed at the elbow, and there is some postural over-extension of the metacarpo-phalangeal joints, with some flexion of the phalangeal joints of all the digits except the thumb." In this experiment the state of the tendon-jerks is not noted, but after a "leg area" extirpation it is noted twenty-four hours after operation that the knee-jerk was increased.

We see, therefore, that there are no essential differences between the changes in motility produced in man, and those produced in the chimpanzee, by isolated ablation of the motor cortex.

The observations of Fulton and Kennard [12] are also essentially identical with these, though their summary and conclusions do not indicate the fact. Thus, they found the same initial widespread loss of movement, the rapid return of movements in the proximal segments of the limb, and the same imperfect restoration of skilled digital movements. Hypertonus, also, appears to have made its appearance in the most paralysed parts of the limb. This is clearly indicated by the statement that the affected arm—even when extensively and deeply paralysed—tends to adopt and to maintain a semi-flexed attitude (a criterion accepted by these observers as indicative of hypertonus). In one instance, Jacobsen [18] reports the persistent adoption of this attitude, while after bilateral ablation of the "leg area," Fulton and Keller [11] state that the postural condition of the lower limbs is "entirely similar with respect to reflexes, adduction of the extremities, lateral deviation of the toes and a tendency to pes equinus; it differs only in one respect, namely, in the *degree*[1] of spasticity" from the state of the legs in human cerebral diplegia (Little's disease).

It cannot be maintained, therefore, that persistent flaccidity is a characteristic of paralyses following ablation of the motor cortex.

The depression of the tendon reflexes is but an immediate effect,

[1] Italic not in the original.

and they may ultimately become exaggerated (Fulton and Keller, p. 108).[1]

A further interest is added to these experiments by the fact that a certain number of animals were subjected, before operation, to training in feeding-box problems (Jacobsen [8]). It was found that, after motor cortex ablation, although the animal appeared to retain the habits previously inculcated, yet the imperfect restoration of hand and finger movements proved an obstacle to their efficient motor execution. This observation corresponds with the findings of Leyton and Sherrington, namely, that "the fore-running idea of the action intended was present and as definitely and promptly developed as usual. All the other parts of the motor behaviour in the train of actions coming under observation seemed accurate and unimpeded except for the role, as executant, of the particular limb whose motor cortex was injured . . . raising the question whether the function of part of the cortex ablated in such cases be not indeed infra-mental" (p. 206).

In conclusion, we find that the state of a limb after ablation of its motor cortex representation corresponds closely to Jackson's description cited earlier. The final result is permanent impairment of skilled purposive movements of the hands and fingers, with some hypertonus in the paralysed parts. The generalization that "general weakness," flaccidity and depression of reflexes are the characteristics of motor cortex ablation is seen not to be in accord with the facts, as recorded by Horsley, Leyton and Sherrington, and also by Fulton and his collaborators. The term "general weakness" has no place in a precise analysis of the loss of movements following cerebral lesions. It takes no account of the nature of the loss, nor of the nature of the cortical representation of movements.

Finally, it is noteworthy that this state of affairs, following motor cortex ablation, corresponds in detail with what Fulton believes to be the sequel of ablation of the premotor cortex, with the single exception of the forced grasping that ensues upon the latter.

(ii) *Ablation of the "Premotor" Cortex.*

The results of ablation of the premotor area, unilaterally or bilaterally, alone and in association with ablation either of the frontal (prefrontal)

[1] A single experiment is sometimes reported by Fulton and his collaborators in more than one paper, and the descriptions sometimes differ on essential points. Thus, Fulton and Keller [11] state that after ablation of the leg area in a chimpanzee, the knee-jerk became "hyperactive" on the third day. Kennard and Fulton [19], reporting the same experiment, say that the tendon jerks were depressed for "several days," do not mention that they ever became hyperactive, and state later in the paper that such hyperactivity was not observed.

region, or of the true motor cortex, are so paradoxical that their interpretation has so far proved impossible, and their correlation with anything observed in the human subject extremely difficult.

This is well illustrated in the observations of Richter and Hines [23]. Using the macaque, they find that while purely cortical excisions of the premotor region are without visible effect, deeper ablations in this region going through to the mesial aspect of the hemisphere as far ventrally as the corpus callosum are followed by the transient appearance of "forced grasping" in the crossed limbs. If such a deep ablation be performed bilaterally, bilateral forced grasping ensues and remains permanently, only to disappear immediately if the corpus callosum be divided. On the other hand, if the entire frontal region anterior to the true motor cortex be ablated on one side, a transient and inconstant "forced grasping" may develop on the opposite side, while if this be done bilaterally, forced grasping ensues and is more persisting.

It appears, further, that deep bilateral excision of the premotor region evokes the appearance of "forced grasping" only when the corpus callosum remains intact, disappearing when this is divided. Richter and Hines were concerned solely with forced grasping and do not therefore record any other motor disturbances following their experimental ablations.

Fulton and Kennard did not carry out all these various combinations of cortical and corpus callosum ablation, and their results, in consequence, tend to make the problem of a premotor syndrome appear somewhat simpler than, in all probability, it really is.

In the chimpanzee [12] unilateral ablation of the premotor area is followed immediately by a total flaccid hemiplegia. Within a few days there appears a tendency to the adoption of a semi-flexed attitude in the arm and feeble forced grasping and some resistance to passive movement. The hemiplegia clears rapidly and completely—within a week—and after this time nothing is seen but "a lag in the initiation of voluntary movement." The forced grasping and hypertonus also disappear.

But it appears that there is a permanent defect remaining, for Jacobsen [18], examining a problem-box trained chimpanzee after the fugitive paralysis of a premotor cortex ablation had passed off, noticed that while the animal showed no defect of fine movements or of co-ordination, it nevertheless appeared unable to "organize" the necessary manipulations and had to relearn them. Thus, he says, "although unilateral premotor lesions did not result in residual motor deficits which

made the execution of fine adaptive movements difficult, the organization of these movements . . . . was greatly disturbed and necessitated post-operative relearning."

This is an essentially different disorder from that described as following motor cortex ablations, and the neurologist will be struck by its resemblance to the motor disorder known to him as *motor apraxia*. Here is no question of a loss of highly integrated digital movements, which is Fulton's interpretation of the condition, but of the animal's *not knowing how* to set about the necessary movements, and having to relearn them. Apraxia is a phenomenon difficult to investigate in an animal and one with which the experimental physiologist is not familiar. This last point is made clear in Kennard and Watt's paper [21] on the results of division of the corpus callosum. They remark that apraxia is a disorder said by clinicians to follow lesions of this structure in man, and add that apraxia "is at best rather a vague term." Yet Wilson's [26] definition of motor apraxia applies admirably to the disorder described by Jacobsen, namely, "inability to perform certain subjectively purposive movements or movement-complexes, with conservation of motility, of sensation, and of co-ordination."

(iii) *Combined Ablation of the Motor and Premotor Cortex.*

The final, residual effects of this appear to have been fairly constant. The immediate result is a severe hemiplegia and slight "spasticity." Transient and feeble forced grasping appeared on the fourth day. The spasticity gradually diminished and the final result appears to have consisted solely in residual hemiparesis with little spasticity (Fulton and Kennard, experiment 5: Baboon). The impairment of hand and finger movements remained severe. This increased depth of residual paralysis appears to have been the sole permanent effect of the addition of premotor ablation to that of motor area ablation.

In the chimpanzee (experiment 8) the results were essentially similar, but in this case both motor areas had been removed, and the spasticity and forced grasping in the arm affected by the combined ablation appear to have been more severe and a little longer lasting.

In both experiments, the forced grasping developed after a latent period of three or four days.

(iv) *Bilateral Ablation of the Frontal Lobe to the Anterior Border of the Motor Cortex.*

This ablation has a special interest for the neurologist in that it reproduces a picture resembling that not infrequently seen in cases of

frontal lobe tumour in man. The animal shows a striking lack of spontaneity, remains motionless for long periods, moves slowly, and when eating continues chewing movements after the morsel has been swallowed (? perseveration). This is bilateral forced grasping, but *no spasticity and no paralysis.* There is nothing to tell us whether or not any dyspraxia was present. This animal passed through a phase of great restlessness. As may be seen in the human subject, the presence of forced grasping is not necessarily accompanied by any spasticity, a finding which does not confirm Fulton's association of these two phenomena as integral components of the premotor syndrome, and suggests that, after all, the appearance of spasticity as a residual symptom requires, and depends upon, a lesion of the motor cortex or of its projection system.

A somewhat similar loss of motor initiative was found by Kennard and Watts [21] to follow division of the corpus callosum alone. No observations of a kind capable of detecting the presence of apraxia appear to have been made in either of the two experiments just referred to.

(v) *Bilateral Ablation of the Premotor Cortex.*

This is the only lesion productive of permanently demonstrable forced grasping, and after this procedure the phenomenon is present bilaterally. This was found both by Richter and Hines and by Fulton and his collaborators.

It may be mentioned in passing that bilateral ablation of both motor and premotor areas produces permanent total paralysis of voluntary movement, spasticity and forced grasping. The condition of the animal is said [12] to be identical with that of the "thalamus animal," but those who are familiar with Magnus's description of this will not be able to recognize any close similarity between the two. The thalamus animal is not, it is true, capable of volitional movements, but as reflex reactions it has a range of motor activities not found in the monkey after the ablation described above.

(vi) *Conclusions.*

Summing up these various observations, it appears that Fulton's generalization that "grave postural and motor disturbances" follow premotor area ablations, scarcely conveys an accurate impression. In macaques unilateral ablation has no visible effect, and in the chimpanzee the fugitive hemiplegia is probably a neighbourhood symptom. Forced grasping in this animal is transient and the sole residual defect is the

one we have provisionally identified with motor apraxia. There is no evidence of an essential loss of skilled movements of the digits.

Combined (unilateral) motor and premotor ablations merely produce a more severe degree of hemiplegia than does ablation of the former area alone, together with the appearance of forced grasping. Fulton suggests that the spasticity of residual hemiplegia in man is due to the addition of a lesion of the premotor projection system to a pyramidal lesion, but the recent examination of human pathological material by Davison and Bieber [8] appears to render this view untenable.

Further, considering the obscure and sometimes conflicting statements about hypertonus or "spasticity" which appear in the various papers of Fulton and his collaborators, a doubt must arise in the mind of the clinical neurologist as to what these experimental observers really understood by the term, how they determined its presence or absence, and finally where they expected to find it in a limb of which only the distal part remained partially paralysed.

For their protocols appear to provide clear evidence of the presence of some hypertonus in the affected limbs of their animals after "motor area" ablations, yet they deny its presence. Purely clinical methods of examining the state of tonus were employed in these experiments, and it is probable that some unfamiliarity with clinical criteria accounts for the discrepancy noted between observation and conclusion. It would undoubtedly be advantageous in such experiments for an experienced clinical neurologist to apply the routine methods of investigation ordinarily employed. It is by such means only that sound comparisons between animal and human material can be made.

With the nature of the phenomena somewhat unsuitably grouped together under the title of "forced grasping" it is not proposed to deal in this paper, but we may say that the observations we have been considering do confirm the conclusions set forth by Walshe and Robertson [25], namely, that there are two components in forced grasping: (1) a volitional component (the so-called "groping" and "grasping" movements); and (2) a tonic contraction of the finger flexors when submitted to stretch, a true proprioceptive reflex action. Fulton [10] objects to the use of the term "volitional" in this connection on the ground that *all* possible movements are reflex, but the value of the objection may be judged by the frequency with which the term is employed in their papers by Fulton and his collaborators, even in connection with forced grasping. It is impossible to escape the use of the term, which has a meaning at once clear and generally understood.

We may conclude, therefore, that the sole symptom we may safely attribute to destroying lesions of the "premotor" cortex is forced grasping, and this in turn is conditional upon the integrity of the corpus callosum. All the other symptoms must be ascribed to disturbance of function in the motor cortex and its projection path. That they are all constantly produced by ablation of this area of the cortex confirms this conclusion. Further, it appears probable that apraxia may be a residual effect of premotor cortex ablation.

IV.—The Definition of the "Premotor" and "Motor" Areas.

In the experimental investigations we have been considering we have seen a tendency to transfer to the "premotor" cortex and its hypothetical "extrapyramidal" projection system functions hitherto accepted as belonging to the true motor cortex and the pyramidal system. If we accept these new views, it is difficult to see what role remains for the latter, and Fulton and his collaborators have not formulated any conclusions on the matter. Now the functions of the motor cortex of the physiologist have been clearly formulated by Leyton and Sherrington on the basis of what still remains the most exhaustive and skilled investigation that has been made. They conclude that these functions are "the upbuilding of larger combinations (of movements) varied in character and serviceable for purposes of different and varied kind. The functional properties of this cortex seem specialized to that end. . . The motor cortex appears to be par excellence a synthetic organ for motor acts . . . an organ for synthesis of movements—and of postures—on a vast scale." But, as we have seen, these are precisely the functions now attributed by Fulton to his "premotor" cortex.

Seeking for some explanation of this extreme change of doctrine, we may find it in part in that use of nomenclature to which reference has been made in the introduction. For when Fulton and his collaborators use the term "motor area" they have in mind the area gigantopyramidalis, which they have *assumed* to be co-terminous with the physiologically delimited motor cortex. As a corollary, all that cortical region lying between the anterior limits of Campbell's intermediate precentral area and the area gigantopyramidalis becomes the "premotor area." This last-named area has its own "extrapyramidal" projection system, the pyramidal tract being relegated to the area gigantopyramidalis.

It seems clear that the very existence of a physiologically differentiated premotor cortex, and also that of the syndrome of this cortical

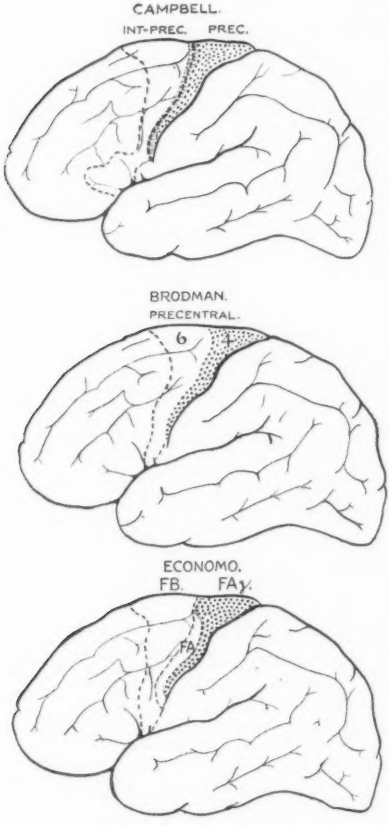
area, depend upon the accuracy or otherwise of this identification of a physiological with a cytoarchitectonic entity. If, in fact, the motor area, properly so named, be more extensive than this assumption allows, the premotor area, with its functions and its syndrome, is largely swallowed up by the motor area.

The solution of the question involves a consideration of both anatomical and physiological evidence. Taking the anatomical aspect first we find that *the precentral area* of Campbell (Economo's area FA) is limited posteriorly by the floor of the fissure of Rolando. According to Economo [9], "near the edge of the hemispheric cleft, this formation reaches in the frontal direction beyond the anterior wall of this gyrus (ascending frontal), and even passes over the precentral sulcus as far as the posterior lip of the precentral or the first frontal gyrus. Farther ventrally, its anterior limits shrink rapidly, so that at the level of the superior frontal furrow it is already behind the front lip of the precentral gyrus; at the height of the second frontal furrow it is again behind the middle of the crown of the precentral gyrus. It then falls back rapidly into the floor of the fissure of Rolando at its ventral end."

But within this precentral area, and less extensive than it, lies the area in which are found the giant cells of Betz (area gigantopyramidalis, FAγ). Dorsally, the anterior limits of this coincide with those of the precentral area (FA), but ventrally to the first frontal furrow "the anterior limit of FAγ recedes much more rapidly than that of FA; so that at the level of the second frontal gyrus the former has reached the posterior lip of the gyrus (ascending frontal), and has sunk completely into the depths of the posterior wall in the region of the third frontal gyrus. That is to say, in the region of F3 giant cells are to be found only in the deep portion of the posterior wall of the precentral gyrus sunk in the fissure of Rolando" [9]. In short, the giant cells lie massed in the dorsal and caudal parts of area FA. Brodmann's "area 4" appears to coincide with Economo's area FAγ, and not with the entire area FA.

The intermediate precentral area of Campbell (Economo's area FB. lies immediately frontal to the area just described. It shows a structure similar to it, except that it contains no "giant cells." It stretches "from the sulcus calloso-marginalis on the median surface over the mesial edge of the hemisphere and the entire frontal convexity as far as the opercular area. Its fronto-caudal diameter lessens considerably as we trace the region ventrally, so that, while it covers several broad strips of the great first frontal gyrus at the edge of the cleft, it is reduced to the precentral gyrus alone in the opercular region" (Economo).

Finally, it may be noted that Brodmann includes his areas 4 and 6 within his "area precentralis," which he correlates with the physiological "motor cortex." Fig. 1 makes these three terminologies clear.



Campbell.—Precentral area = Betz cell area, plus a narrow zone of transition between it and the intermediate precentral area.

Brodmann.—Precentral area = both the above areas. Betz cell area = area 4, and the region anterior to it is area 6. Both together are named precentral area and are thought by Brodmann to correspond to the physiologists' "motor cortex."

Economo.—Area FAγ = Betz cell area. Area FA = entire precentral area, which is of greater extent. FB = area frontalis agranularis. FA and FB together correspond to the "electro-motor zone" of the cortex.

FIG. 1.—Of these three histologists, Campbell alone identifies the area gigantopyramidalis with the motor cortex of the physiologist. Brodmann says: "Auch hier fällt das 'Reizfeld' räumlich fast genau mit meiner Regio precentralis, also den beiden cytoarchitectonischen Feldern 4 und 6 (nicht etwa nur der Area gigantopyramidalis), zusammen."

This somewhat lengthy recapitulation of the different architectonic delimitations of these cortical regions is essential before we come to consider the limits which physiological experiment has placed to the "motor cortex." It is seen that an identification of this region with the area gigantopyramidalis is nowhere made by the physiologist, nor has any histologist except Campbell explicitly made it.

Leyton and Sherrington [22] have shown that the true motor cortex has no sharply defined anterior limit, and have described at great length and in detail the various physiological and individual factors which determine its anterior limits. They write: "It is instructive, therefore, to compare the limits of the motor field as determined by faradization in those anthropoids with his (Campbell's) 'precentral area' determined by cell and fibre lamination. The posterior borders of the two as delimited by these two different methods seem to agree so closely that there can be little doubt that as regards that limit the two fields or areas are the same. In regard to the anterior border, the motor field's boundary seems to lie, especially in its lower two thirds, farther forward than does that of Campbell's precentral area. The anterior boundary, as determined by faradization, is, however, not a sharp one, and its situation seems to vary somewhat from specimen to specimen. As placed by us, it certainly appears to lie for the most part in the intermediate precentral area of Campbell. Opposite the 'arm area' it lies not far behind the anterior boundary of the intermediate precentral area, but opposite the 'leg area' more considerably so. Opposite the 'face area' it lies very much further behind the anterior limit of intermediate precentral area, although in front of anterior limit of the pure precentral area of Campbell. Campbell, in his original description, furnishes a number of arguments in favour of his intermediate precentral type of cortex possessing motorial functions, though differing from the precentral type or motor cortex pure. The gradual shading off of the pure motor field in the anterior direction, as experienced in our observations, and the variability of its anterior edge, as mentioned above when faradized under different experimental conditions, seem to us to lend support to his contention, although the latter was put forward on other evidence" (p. 158).[1]

It is clear, therefore, that the identification of the area gigantopyramidalis, or even of the entire precentral area, with the "motor cortex" of the physiologist is erroneous, since the last-named area

[1] Yet another experimental investigator has expressed himself in the same sense. Thus, Rothmann says: "Vor allem ist die mit Riesenpyramidenzellen besetzte Area gigantopyramidalis weder mit dem elektrischreizbaren Rindenfeld noch mit der motorischen Region der Grosshirnrinde noch endlich mit dem Ursprung der corticospinalen Bahn zu identifizieren. Das geht nicht nur aus den Ergebnissen am niederen Affen, sondern auch aus den, vor allem mit Hilfe der Rindenextirpation, beim Anthropoiden und Menschen gemachten Beobachtungen mit Sicherheit hervor." (Über die physiologische Wertung der cortico. spinalen (Pyramiden-) Bahn. *Arch. f. Anat. u. Physiol.*, Physiol. Abteil., 1907, 2-17 Nothing that has since happened requires any modification of the views herein expressed.

includes a considerable extent of the histologically delimited intermediate precentral area.

Further, it is of interest that these physiological observations afford no ground for thinking that the motor functions of that part of the intermediate precentral area included within the motor cortex (properly so-called) differ in any way from those displayed by the precentral cortex.

Parallel with the assumption that the motor cortex, properly so-called, is identical with the area gigantopyramidalis goes another: namely, that the pyramidal tract arises solely from giant cells within this area.

Some twenty-five years ago, Horsley, in a paper already referred to, gave adequate reasons for rejecting any such assumption. He said "that to include the whole efferent or motor area as determined by excitation we must take two of Campbell's regions, both his intermediate precentral and his precentral areas, although he wishes, apparently, the term "motor" to be restricted to the latter. This suggested restriction of the term "motor," namely, because the giant cells of Betz are to be found only in a certain (the major) portion of the precentral gyrus, cannot be justified, since it would exclude the motor centres for the face, larynx, pharynx and eye muscles, as well as part of the representation of head movements. It also disregards the anatomical rule that an efferent or motor cell varies in size according to the distance the axone has to travel in the central system—for example, the largest pyramids in the precentral gyrus are in the leg area."

But there are other cogent reasons for rejecting this restriction of the pyramidal tract to the axones of giant cells within the Betz cell area. The fact that the cells to which the descriptive term "giant" has been applied lie solely within this area is not a proof that the pyramidal tract arises only within it. The first precise study of its origin is that of Holmes and Page May [15], and while they accept the "giant cell" origin of the pyramidal tract, they accept wide variations in size for these cells, variations which they correlate with differences in the calibre of the cortico-spinal fibres. It is noteworthy that the area of distribution of these cells, in man and in chimpanzee, which they figure in their paper (figs. 7 and 8) is more extensive in an anterior-posterior direction than is seen in the cortical maps of Campbell (*cf.* Plate IX) and of Economo. They remark that this distribution corresponds with the physiologically delimited motor area,

and it is apparent that the degree of correspondence between the two is greater in these figures than in those of the other authorities referred to.

Clearly, the statement that the "giant cells" alone give rise to pyramidal fibres has no meaning unless we are agreed as to what constitutes a giant cell. On examination we find that our standards on this point are various, arbitrary and without discoverable physiological value. According to some authorities the standard of identification is purely dimensional, and Brodmann [3] cites several such standards as given by different observers. Economo [9] has yet another standard and states that "all pyramidal cells larger than 60 or 100/25 or 60 μ are to be considered as giant cells." He is, however,

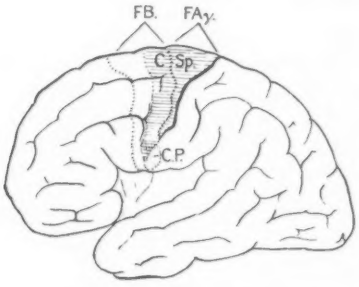


FIG. 2.—(Economo and Koskinas. Figs. 87 and 92). Showing the relation of the origin of the cortico-spinal (C.Sp.) and cortico-pontine (C.P.) fibres to areas FAγ and FB. The area of distribution of the pyramidal cells of 3rd and 5th cortical layers from which these pathways arise is cross-hatched.

careful to avoid any physiological inferences from what can be no more than a purely descriptive convention, for he states that "axones of other large pyramidal cells in area FA" give rise to pyramidal tract fibres, and he points out that in conformity with a general law in the anterior half of the cortex, the largest cells lie in the dorsal and caudal portions of each histologically differentiated field. Bevan Lewis [2] accepts as giant cells, cells which are of markedly smaller dimensions than those allowed by Economo, and as we have seen Holmes and Page May also accept wide variations in size and indicate the difficulties involved in determining the anterior limits of their distribution. In discussing this question of the cells of origin of the cortico-spinal pathways, Economo and Koskinas in their large work on the cytology of the cerebral cortex express themselves quite emphatically, saying, "es vielleicht doch ein Trugschluss ist, in den man gar leicht verfällt, wenn

man im allgemeinen nach der Grosse der Zellen auch ihre Bedeutung und physiologische Dignität schliessen durfen glaubt."

The fact that "giant cells" have been described in the frontal and superior parts of the postcentral convolution by all observers from Betz to Economo, in the same cortical layer as the giant cells of the area præcentralis gigantopyramidalis, is an apt commentary upon this aphorism. The authors illustrate what they believe to be the area of distribution of the cells of origin of these pathways and show that this is not co-terminous with the area gigantopyramidalis (fig. 2).

In short, the "giant cell" is a dimensional and not a physiological entity and we can scarcely blame the histologist if it has come to be regarded as the latter.

Finally, we have the recent investigations of Hoff and Hoff [14] which appear to indicate that the area 6 of Brodmann, Campbell's intermediate precentral area, also furnishes fibres to the pyramidal tract.

In short, the hypothesis that the pyramidal tract derives solely from cells within the area gigantopyramidalis is as unfounded as that which identifies this area with the motor cortex of the physiologist. Both run counter to experimental and histological facts of observation.

The terms "motor" and "premotor" are not interchangeable with the terms "precentral" and "intermediate precentral" (or with "area 4" and "area 6"), and the conception of two sharply differentiated cortical regions, each with its own projection system, and each with widely differing functions, is illusory. The true motor cortex includes much of Fulton's "premotor area" and the pyramidal system arises within all parts of it.

That a fronto-pontine tract arises also somewhere within the more anterior parts of this area is another matter, and the functions of this path remain to be elucidated.

Added to the confusion created by this inexact use of nomenclature is yet another factor making for misunderstanding. As we gaze at any one of the various cortical maps, such as Campbell's, Brodmann's, or that of Economo, we may easily gain from them the impression that the cytoarchitectonic boundaries thereon depicted are as clear-cut, constant and immovable as the field boundaries we may see from an aeroplane, and that we may use them as we would a physiographer's map. They have not this precision nor do their authors claim it for them. They represent simply a composite picture and do not reveal those individual variations and those zones of transition upon which all

histologists insist. Moreover, there is a deliberately produced simplification about them, and they represent as though upon the exposed surface of the convolutions regions that are in fact buried in the sulci. This is strikingly the case with the area gigantopyramidalis, as a comparison between Campbell's Plates I and IX will reveal. In its lower half this area is wholly buried in the anterior wall of the fissure of Rolando, and would scarcely appear on the surface in a picture which did not distort the cerebral contours.

The practical bearing of this digression is that while it may seem from a study of the cortical maps to be a simple matter to ablate a portion of the area gigantopyramidalis, leaving the region immediately anterior to it intact, in practice the difficulty of a pure ablation of the area must be almost, if not quite, insurmountable. Yet, this is in fact what a pure motor cortex ablation means in Fulton's hypothesis, though not in his experiments. One has only to study the neurological literature dealing with the interpretation of symptoms to see how frequently an undue preoccupation with pictures, and a failure adequately to consider the organ they so imperfectly represent, has proved adverse to fruitful investigation.

That these various points we have discussed are not merely academic objections without practical bearing upon our subject, but are of the greatest significance, may be seen in a case of so-called " premotor cortex ablation " reported by Bucy and Buchanan [5]. The case was that of a child with a residual spastic hemiplegia, athetosis of the affected arm, and recurrent epileptiform fits. To abolish the athetosis the writers excised that portion of the pre-central convolution which, on faradic stimulation, yielded movements of the affected limb. The area they excised is seen from their diagram to lie wholly within the " motor cortex " of the physiologist, and almost wholly within the precentral convolution, yet because it lies anterior to the area gigantopyramidalis they describe it as a " premotor " ablation, for they regard the area gigantopyramidalis as identical with the physiological ".motor cortex."

The case therefore stands on record in the literature as an example of the abolition of athetosis by ablation of the premotor cortex, and as an illustration of the destruction of an irritable focus (in this area) which was discharging disorderly impulses along an extrapyramidal path to the ventral horn cells. Manifestly these conclusions rest upon wholly erroneous premises.

Conversely, if the authors' localization of their lesion in the premotor cortex were correct, forced grasping should have ensued in the affected hand. It did not ensue.

In this discussion we have assumed that the cytological and physiological factors are essentially the same in man and in the anthropoid, and all the evidence indicates that such an assumption is justified, for the histological areas are in all important details the same in each case, and as far as we know the "excitable" area of the cortex is also identical.

V.—General Conclusions: The Nature of the Cortical Representation of Movement.

In the series of papers dealing with a so-called syndrome of the premotor cortex, which we have passed under review, many problems have been raised with which we have not attempted to deal. Such are the nature of the complex of phenomena known as "forced grasping," the bilaterality of cortical representation of movements [6], the excitability of the premotor cortex, the occurrence of vasomotor disturbances and the cytoarchitecture of the premotor area [4].

To have considered all these diverse questions would have unnecessarily confused the three simple problems we set out to discuss; namely, the evidence for the occurrence of a recognizable syndrome of the premotor cortex, the characters of the syndrome of the motor cortex, and the precise meaning to be attached to the terms "motor" and "premotor."

Perhaps the last problem should have been considered first, for if these two terms do not embody precise and consistently employed conceptions, no hypotheses based upon them are likely to be valid. In the event we have found that these two terms have been used in a wholly arbitrary sense, and in so far as the term "motor cortex" is concerned, in a sense essentially different from that understood by all other workers in this subject. We have seen that this term is a physiological one and cannot be used to indicate either the precentral area, nor that part of it known as the area gigantopyramidalis. It includes the entire precentral area and a considerable extent of the intermediate precentral area (Campbell), and the failure to recognize this, although it has been clearly laid down by numerous authorities, has largely vitiated the evidence upon which it has been sought to erect two distinct syndromes, one of the "motor" and the other of a "premotor" area.

An even larger question is raised by the conception of the cortical representation of movements embodied in the papers of Fulton and his collaborators. It is necessary that we should try and define

what we may understand by the expression "cortical representation of movements."

Various views on this subject compete for acceptance. On the one hand, we have the view exemplified in the writings of Campbell—and adopted by Fulton and his collaborators—which makes of a cytoarchitectonic field (in this case, the area gigantopyramidalis) a physiological entity. This field is a kind of mosaic of points each of which represents a single muscle, or a muscle group (or even perhaps a movement, for it is not quite clear what Fulton holds on this point). Apparently only simple movements are thought to result from the activity of this region. Indeed, it would seem that what is called "motor power" is—in some undefined and indefinable way—represented here rather than "movements." This field is sharply bounded in every direction, and as we cross its anterior border we enter abruptly another cytoarchitectonic-physiological field. In this are represented movements of quite another order, exemplified by the "highly integrated movements of the digits," and here representation is in a measure bilateral.

This field—or organ—is also sharply limited by surrounding and differentiated fields, whose functions presumably are equally sharply differentiated.

The essential feature of this conception of cortical motor representation is that this embodies two quite distinct mechanisms, each co-terminous with a distinct cytoarchitechtonic field, each with its own separate functions, and each sharply circumscribed by anatomical boundaries. This is a conception that might be attractively depicted in a diagram, and we may be sure that it is in a diagram only that it can have any existence.

At the other extreme we have the view that is exemplified in the writings of Lashley. Here, any topographical localization of function in the cortex is frankly regarded as a fiction. Even the representation of the retina in the calcarine cortex is questioned by this school, whose doctrines are in a measure a reversion to that early view of Taine (cited by Hughlings Jackson) for whom "the brain is a kind of polypus, whose elements have the same function."

Between these extremes stands the conception of cortical representation formulated by Jackson. Apparently, this is as far ahead of much current neurological thought as it was in Jackson's own time, and it obtains no attention from either of the two schools we have mentioned. Perhaps the views of Lashley are a natural reaction from the rather naïve "jig-saw puzzle" hypotheses of cortical localization, but it seems

probable that in Jackson's views is to be found the common ground on which both schools might meet and resolve their differences.

Jackson's doctrines nowhere find a single comprehensive expression, but are to be found scattered throughout his various papers. The following brief statement embodies—it is believed—their essence.

It is not necessary to recapitulate his conception of three levels of function, highest, middle and lowest, for his teachings on this point are widely known. It is particularly the highest and middle levels which concern us here, for the cerebral cortex provides their anatomical substratum. The excitable motor cortex of the physiologist is the seat of the "middle level" of motor function. It has been evolved out of the lowest level, and in it are re-represented, or re-coördinated, the simple and general movements represented in the lowest level. This re-representation consists in the synthesis of complex and special movements out of the simpler elements of the lowest level, and the experimental observations of Leyton and Sherrington have lent detail and confirmation to this conception.

For Jackson, the "præfrontal region" is the seat of his highest level. Here there takes place a further analysis and synthesis of movements represented in the middle level into the most complex and special movements of which the organism is capable.

There are no "abrupt" localizations in these two levels, and *all* movements are widely represented throughout them. Thus, Jackson says "the 'arm centre' in the Rolandic region is for me a centre representing movements of all parts of the body, but yet movements of the arm very much more than any other movements." Again, "the central nervous system knows nothing of muscles, it only knows movements. . . . There are, shall we say, thirty muscles of the hand, these are represented in the nervous centres in thousands of combinations—that is, as very many movements. It is just as many chords, musical expressions and tunes, can be made out of a few notes." He gives examples of this multiplicity of representation, and a familiar example will occur to the clinician. Thus, in a partial hemiplegia, voluntary extension of the wrist is often lost while the power of voluntary clenching of the fist is retained. But in the latter movement the wrist is strongly extended. This is to say, one representation of extension of the wrist is lost, but another and slightly different one (as a synergic movement) remains. Again, conjugate deviation of the eyes has no representation within the true motor cortex as a primary movement, but only as secondary to rotation of the head. Its representation as a primary movement lies elsewhere in the second frontal convolution.

These various representations necessarily require a great "quantity" of grey matter, and Jackson says "it is equally obvious that the larger quantity of grey matter representing numerous different movements must be made up of a great number of separate parts. Each movement, so far as it differs from all others, must have so far special representation in the nervous centres. Greater differentiation of function implies greater physical separation, however little different the movement may be from other movements, and however much of it may be a recoördination of other movements. So far as there is a degree of independence of movement, so far must there be a degree of separateness of representation of that movement by different cells in the nervous centres. And yet, of course, the separation is not isolation; on the contrary, the greater the differentiation, the more complete the integration of the different elements, for they have to act together or in succession . . . I do not believe that nervous centres represent limited regions of muscles, nor even isolated groups of movements . . . any part, especially such a one as the hand, is represented in innumerable places."

This quality of representation accounts for the lack of symptoms after local destroying lesions, and when any loss of function does ensue from such a lesion recovery takes place not because other units have taken on functions they never had before, but because those units, having functions closely similar to those of the units destroyed, they can act nearly as well for the functions of both. This is Jackson's *principle of compensation*.

But on this basis compensation can never be absolute, a fact which is also familiar to the clinician. Thus, the victim of a cerebral thrombosis who appears on routine examination to have made a perfect recovery is nevertheless usually aware that some special movements of the affected hand and digits are gone for ever. If he previously played some musical instrument, he finds that his hand has lost some of its cunning for the task—some of his "special" movements have been lost.

It is perhaps not surprising that those whose studies of the effects of cerebral lesions are confined to the monkey, or to some lower animal, should suppose that recovery can be absolute. The animal, with its scanty repertoire of special movements has not so much to lose, and the really detailed examination of its motor functions is necessarily difficult, if not impossible.

We see, then, that on this view of cortical localization the absence of symptoms after a local destroying lesion does not mean that there is

no local representation. On the contrary, it bears witness to the complexity and highly specialized character of that representation.

This theory of the cortical representation of movements postulates no "jig-saw" puzzle of rigidly defined, separate local elements on the one hand, nor an undifferentiated cortex acting by mass on the other. These opposing notions we might almost define as being "differentiation without integration," and "integration without differentiation" respectively. Jackson's conception allows of the special representation of every possible movement, and is compatible alike with the absence (or paucity) of symptoms after local destroying lesions, and with the spread and sequence of convulsion in states of instability of grey matter. It truly represents "differentiation with integration," and would appear to be the only possible valid generalization of all the varied facts of clinical and experimental observation.

And while Jackson placed his highest level of cortical motor function in the frontal lobe anterior to the excitable cortex, he did not separate it from the middle level by any such arbitrary cytological boundaries as are inherent in the view postulated by Campbell and adopted by Fulton.

The conclusion we have reached, then, is that neither on anatomical nor upon physiological grounds can we accept the division—of structure and of functions—made by Fulton of the cortical region lying anterior to the fissure of Rolando. It remains to summarize the actual facts of observation recorded by him and his collaborators.

As far as it is possible to recognize two distinct syndromes resulting on the one hand from ablations within the precentral area, and on the other from ablations of the region immediately anterior to this, it appears that :—

(1) Ablation of the precentral gyrus, or of that part of it lying next to the fissure of Rolando, is followed by a hemiparesis conforming in character to Jackson's description given earlier, and resembling the slighter degrees of hemiplegia in man. Some hypertonus has finally developed in the most paralysed parts of the limb and the tendon-jerks have shown a corresponding increase. After cessation of recovery there has been a residual loss of some special movements of the digits.

(2) Ablation of the region lying immediately anterior to the last considered is followed in the chimpanzee by a very fugitive hemiplegia, which is either a "neighbourhood symptom" or more probably due to actual encroachment of the lesion on the motor area, properly so-called. The sole residual defect appears to resemble that known to clinicians

as motor apraxia. Permanently enduring forced grasping does not ensue except in bilateral lesions of this region.

(3) Ablation of the frontal convolutions anterior to both the preceding regions is followed, not by paralysis or spasticity, but by a loss of spontaneous motor activity on the part of the animal, with a tendency to perseveration and slowness of movement. Phases of restlessness may also appear.

(4) Forced grasping may appear, both in man and in apes, apart from either paralysis or spasticity, and cannot therefore be regarded as an integral part of a syndrome in which all three are invariably present.

(5) The so-called "premotor syndrome" is predominantly a syndrome of the true motor cortex and follows lesions within this experimentally delimited region.

(6) There is only one kind of hemiplegia, though several degrees of this, and it is seen only in association with lesions involving the true motor cortex and/or the pyramidal tract.

(7) The more extensive the destroying lesion of the cortex in the region immediately anterior to the fissure of Rolando, the more severe the degree of hemiplegia resulting and the more marked the residual defect. Accompanying this severe degree of hemiplegia there is commonly more marked hypertonus.

In conclusion, there remain many problems in determining and analysing the disorders of motor function which ensue upon lesions of the anterior parts of the frontal lobes. Some of these disorders have been glimpsed in the course of the experiments we have considered and many others are familiar to clinicians. It is hoped to attempt some discussion of these in a subsequent paper.

Addendum.

Since this paper was written another contribution to the subject has appeared (*Proc. Californian Acad. Med.*, 1933-34), in which Fulton gives for the first time a comprehensive definition of what he understands by the term "motor cortex." It is as follows: "The motor area is defined histologically as the region of the cortex containing in its fifth layer the large cells of Betz. It should be emphasized that the limits of the motor area are determined by its cellular structure and not by its electrical excitability."

The author does not indicate to his readers that the above usage of the term in question differs essentially from that hitherto generally adopted. It is perhaps better, therefore, not to regard it as a scientific definition but as something in the nature of a private ruling that a term

which has always rightly been applied to a certain cortical region in virtue of certain properties revealed by it, shall henceforth be applied to something different; namely, to a cortical region which contains pyramidal cells exceeding certain arbitrarily determined and inconstant dimensions. Such a reading of the term "motor cortex" lacks both physiological value and anatomical precision, and cannot be made the basis of any hypothesis of cortical motor functions.

However, in concluding the discussion of this subject it may be noted that Fulton employs this special definition of the "motor cortex" only in connection with the investigations considered in this paper. Where he is not concerned with the functions and syndromes of the premotor cortex, he appears to employ the term "motor cortex" in the generally accepted sense. Thus in a paper with Dusser de Barenne (*Journ. Cell. and Compt. Physiol.*, 1933, **2**, 399), the terms "motor" and "excitable" as applied to the cortex are used as synonymous, and figures are given in which the motor cortex is depicted as of considerably greater extent than the area gigantopyramidalis. In these circumstances, it may not be an unjust inference that theoretical considerations have had undue weight in the formulation of the arbitrary definition to which objection has been raised here.

Further, the paper contains what appears to be an important modification in the description of the "premotor syndrome." As originally described, the essential defect symptom was a loss of highly integrated digital movements, but this symptom is now said to be in the nature of "an intellectual deficit" in consequence of which the subject has *forgotten how* to perform certain learned movements and has to relearn them. While this mode of expression involves a flight to psychological terminology, it does indicate what is probably a more correct assessment of the motor defect described by Jacobsen after ablation of the premotor area in the chimpanzee. Nevertheless, it profoundly modifies the original description of the premotor syndrome. Further, since Fulton regards the premotor cortex as the cortical representation of the "extrapyramidal motor system," we have the paradoxical conclusion that a destroying lesion of this system produces as its characteristic symptom "an intellectual deficit." This involves an entirely new conception of the functions of the extrapyramidal system.

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THE DISORDERS OF MOTOR FUNCTION FOLLOWING AN ABLATION OF PART OF THE "LEG AREA" OF THE CORTEX IN MAN.

BY F. M. R. WALSHE.

In the preceding paper (p. 49) the results of a partial, destroying lesion of the physiologically delimited motor cortex were summarized as follows: (i) The immediate result is a widespread paralysis of movements of the affected limb, the special and varied movements of the distal part of the limb being most severely paralysed; (ii) the large and simple movements of the proximal part of the limb recover early and completely, the special and more varied movements of the distal part recovering more slowly and less completely, so that some of them are permanently lost or impaired; (iii) hypertonus develops in the most severely paralysed parts of the limb; and (iv) the tendon-jerks become and remain increased.

This state of affairs corresponds to the description given by Jackson of partial hemiplegia and to the findings of Leyton and Sherrington in the chimpanzee and of Horsley in man.

It was noted, however, that Fulton employs the term "motor cortex" in a special sense, restricting it to the area giganto-pyramidalis. The syndrome summarized above he attributes to a lesion of the "premotor cortex" and of its hypothetical extrapyramidal projection system. He would therefore regard the cortical ablations of Leyton and Sherrington and of Horsley as predominantly "premotor."

From what we have learned of the distribution of the area giganto-pyramidalis it will be apparent that a pure ablation of this area is practicable only at its superior extremity, where its antero-posterior extent is considerable—some two centimetres in the adult human brain—and is not practicable elsewhere since the area in question is buried in the anterior wall of the fissure of Rolando lateral to the superior genu. Indeed, the motor representation of hand and finger movements in the cortex lies almost wholly frontal to the area gigantopyramidalis and contains relatively few "giant cells." That is to say, the representation of these movements is a function of Fulton's "premotor cortex" and its

extrapyramidal projection system; a corollary to their hypothesis which Fulton and his collaborators do not appear to have appreciated.

If, then, in man we are to study the results of a pure "motor cortex" ablation (in Fulton's special sense) it can only be by the ablation of the superior extremity of the area gigantopyramidalis, of that part wherein movements of foot and toes are represented. In this region such an ablation is practicable.

Through the kindness of Dr. Gordon Holmes the writer has had an opportunity of examining, both before and after operation, a patient in whom an ablation of the superior extremity of the area gigantopyramidalis was performed. He has also enjoyed the advantage of access to Dr. Holmes' exhaustive notes of the case made over a long period of time.

The ablation was one to which it cannot be objected that it encroached upon Fulton's "premotor cortex." Moreover, the case had the unique merit that the motor and reflex condition of the lower limb was entirely normal prior to the ablation. Thus all the changes effected in the limb by the ablation may be attributed to it. In this the case had advantages over Horsley's and Bucy and Buchanan's cortical ablations in man, in both of which the limb was not wholly normal before operation.

We may precede the record of this case by stating that the results of the ablation corresponded exactly with the syndrome summarized in the opening paragraph of this paper, and in no way resembled Fulton's hypothetical syndrome of the "motor cortex" in man.

E. L., an intelligent and educated girl, aged 11, first came under observation in 1933 with the following history: In 1929, at the age of 7, she began to be subject to attacks of "spasm" in the left foot and leg. These recurred with varying frequency until 1933, when she came under observation. They occurred at night. She awoke to find the left foot and leg rigid and her "head in a whirl." If she got out of bed she found the left leg so weak that she fell. Sometimes, also, the left arm "went limp" so that she dropped anything held in the left hand.

Enquiry revealed that the attacks were of three grades of severity:—

Severe attacks.—She wakes up, the left leg is rigid, the foot rigidly plantar flexed and inverted. Consciousness is never impaired, but sometimes she feels that she cannot breathe. The right leg may also go rigidly straight, but the face and right arm are never affected. In a few seconds the left leg "jerks and trembles." Headache comes on during the attack and may persist for some hours. The attacks last for from thirty to seventy-five seconds. When it subsides the left leg remains weak for some minutes and feels "like a strange piece of warm flesh."

Milder attacks.—Onset as above, but the left leg only affected. The foot

goes rigid, the knee may be rigidly extended or may draw up. The attack lasts for from twenty to sixty seconds. If standing she has to seek support since the left leg is very weak, and so remains for a short time.

Slightest attacks.—These consist solely in a feeling of numbness in the leg and foot lasting for some seconds and accompanied and followed by weakness of the leg. There is neither stiffness nor movement of the leg.

Examination at this time (1933) revealed no abnormal physical signs in the nervous system. The left leg was normal in every respect, but on one occasion a slight attack was observed and was found to be followed by the transient appearance of an extensor plantar response in the left foot.

Repeated examinations over a period of three weeks failed to reveal any abnormality in the left leg, or elsewhere.

In July, 1934, the attacks increased greatly in frequency, as many as fifty a day being observed. An attack invariably occurred at the moment of falling asleep. Repeated examination of the nervous system revealed no abnormal physical signs.

In November, 1934, the attacks were becoming more severe and occurred at all times. The leg was more rigid in the attacks. She fell if standing unless she grasped a support. The left arm tingled, went stiff and shook in the more severe attacks. The face remained unaffected, and consciousness was never impaired. At times the left foot "felt funny" and the toes were not under complete control. From three to eight attacks occurred daily.

Repeated examination in the intervals between attacks revealed no abnormal physical signs in the nervous system; the movements, tone, sensation and the reflexes in the left leg being normal.

In December, 1934, from four to six attacks occurred daily. They began with an indescribable feeling in the left toes and foot, which ascended the limb to the waist. This might pass off without any ensuing spasm, but sometimes the foot began to tingle, then to draw up. Sometimes the knee drew up also. The left arm became stiff and weak. Clonic jerks developed in both arm and leg. Some transient weakness of both arm and leg ensued. In what the patient called "all over attacks" the right limbs also jerked, but less violently than the left. The face was never involved, and speech and consciousness remained intact.

Examination on one occasion shortly after an attack revealed increased tendon-jerks in the left leg, and a tendency to ankle clonus. The abdominal and plantar reflexes were all normal. There was a defect of postural sensibility in the left toes, but other modes of sensation were normal.

On all other occasions the state of the limb was normal—and so remained until after operation.

On December 20, 1934, the right cerebral cortex in the Rolandic region was exposed (Mr. Julian Taylor). No abnormality of appearance, tension or consistency was found. The "arm area" was found by faradic stimulation to be unexpectedly high on the ascending frontal convolution, and the area from which movements of the foot and toes could be elicited lay mainly on

the mesial aspect of the hemisphere. This region was then excised by a diathermic knife.

Subsequent *histological examination* (Dr. Greenfield) of the fragment of cortex removed (1·5 cm. in antero-posterior dimensions) revealed that its caudal portion had the structure of granular post-central cortex, but anterior to this and to the extreme frontal end of the fragment numerous Betz cells were found. Thus, the frontal limits of the area gigantopyramidalis were not transgressed.

Seven hours after operations.—The patient was fully conscious and comfortable. There was total loss of voluntary movements of foot and toes, left ankle clonus and a left extensor plantar response. There was impairment of postural sensibility in the hallux.

Thirteen days after operation (re-examination by G. H. and F. M. R. W.).—There is a trace of paresis of the left lower face on smiling, but not on movements carried out to order. There is slight paresis and slowness of finger movements, especially of isolated finger movements. The outstretched left arm droops slightly. Its tendon-jerks are brisker than those of the right arm. The tone is normal. The abdominal reflexes are present bilaterally, but are brisker on the right side.

The left lower limb is not wasted. Its vascular condition is normal. There is total loss of voluntary dorsiflexion, inversion and eversion of the foot. There is no dorsiflexion of any of the toes, but feeble plantarflexion of the two outer toes only. At the knee both flexion and extension are weak, the former more so than the latter. At the hip extension and adduction are slightly weak, flexion and abduction are weaker. All movements of the limb are slow and clumsy, and she can just fling up the extended leg so that the heel clears the bed by about 6 in. The right knee and ankle jerks are normal, the left greatly exaggerated and there is clonus at the left ankle. The right plantar response is flexor, the left extensor. There is no hypertonus of the hip muscles, but slight of the knee extensors. There is considerable spasticity of the dorsiflexor muscles of the ankle and foot.

There is slight impairment of postural sensibility in the toes, but cutaneous sensibility is normal.

Fifty days after operation.—Movements at the hip are now of normal strength, knee flexion remains slightly weak. There is weak dorsiflexion, inversion and eversion of the foot. All toe movements are defective. Left ankle clonus and increased knee and ankle jerks remain. The plantar response is extensor. Sensibility is unchanged since last observation.

Summary.—Circumscribed ablation of that portion of the area gigantopyramidalis from which movements of foot and toe could be elicited on faradic stimulation is followed by total loss of all movements of the foot and toes, and by impairment of all movements of the limb—least of those of the proximal segment of the limb. Rapid recovery of movements of the proximal part of the limb ensued, but movements of

the foot and toes still remained grossly defective after fifty days. Hypertonus developed early in the most paralysed parts of the limb, and tended to increase in degree with the passage of time. Increase in the tendon-jerks was also an early phenomenon, clonus appearing within a few hours and persisting undiminished after fifty days. The plantar response was extensor in type from the outset. There was an initial "neighbourhood" paresis of the face and arm, which soon disappeared.

Conclusions.

In this case of localized convulsion of the left leg, beginning in the foot, the limb was in every respect normal in movements, tone and reflexes up to the moment of operation. The residual abnormalities that are described above may thus be attributed in their entirety to the cortical ablation.

Both macroscopically and microscopically the lesion was within the area gigantopyramidalis, and therefore is—even in Fulton's arbitrary connotation—a pure "motor cortex" ablation. The residual state of the limb was one in which restoration of the movements of the foot and toes remained incomplete, hypertonus and increased tendon-jerks appeared, with ankle clonus and an extensor plantar response.

This is the syndrome described by Leyton and Sherrington in the chimpanzee and by Horsley in man, and corresponds to the picture of partial hemiplegia given by Jackson in respect of the loss of movements. It does not resemble Fulton's "syndrome of the motor cortex" in man, which we may therefore conclude to have no real existence.

With the single exception of "forced grasping" we may also conclude that Fulton's syndrome of the "premotor cortex" in man is in reality a syndrome of the true motor cortex, and has nothing to do with a histologically and physiologically differentiated "premotor cortex" and its extrapyramidal projection system.

The writer wishes to express to Dr. Gordon Holmes his thanks for the opportunity of observing and recording this case.

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DIABETES INSIPIDUS.

BY J. H. BIGGART.

(Laboratory of the Scottish Asylums Board, and Department of Pathology, Edinburgh University.)

SINCE Thomas Willis [38] in 1674 differentiated between diabetes mellitus and diabetes insipidus many theories have been evoked to explain the pathogenesis of the latter disease.

Following the recognition of a diabetes insipidus the issue was made rather involved by the description of oxaluric diabetes, hippuric diabetes, phosphaturic diabetes and albuminuric diabetes. However, in 1841, Lacombe [23] gave a good clinical description of diabetes insipidus, and with the subsequent work of Bernard [4], this was established as a definite clinical syndrome.

Since that time there have been three main epochs in the history of the syndrome. The first dates from 1860 when Bernard produced a similar syndrome in rabbits by puncture of the floor of the fourth ventricle. Such a puncture produces a polyuria of low specific gravity which, however, clears up in a few days. Bernard's results were verified by Eckhard [13], Jungman and Meyer [20], and amplified by those of Kahler [21], who succeeded in producing a permanent polyuria by the injection of silver nitrate solution into the medulla in the neighbourhood of the restiform body. More recently Dresel and Lewy [11] came to the conclusion that the area concerned was in the floor of the fourth ventricle, medial to the spinal tract of the trigeminal nerve, ventro-medial to the restiform body and dorsal to the nucleus of the seventh nerve. When such were the results of physiological experiment it is not surprising that the attention of pathologists was focused on the floor of the fourth ventricle to the exclusion of the rest of the brain. Thus Mosler [27] describes a case associated with a tumour of the fourth ventricle. There is no description of the hypophysis. Fink [15] gives a review of the autopsy reports during this period which shows the absence of microscopic studies, and the varied nature and sites of the lesions deemed responsible.

Following the work of Schäfer and Magnus [26 and 34], and Herring [18] on the active principle of the posterior hypophysis and its

relation to diuresis the second period in the history of the disease may be said to have begun. At first it was believed that the posterior lobe extract produced a diuresis, and hence that diabetes insipidus could be explained on the assumption that this gland was overacting. The importance of the hypophysis as an ætiological factor was further demonstrated by the experiments of Cushing [8] (1910-1914), who succeeded in producing the syndrome by hypophysectomy. Whilst the importance of this gland in the production of the syndrome became accepted, there remained some doubt as to whether hypo- or hyper-function was the basis of its action. Finally, in 1913, Farini [14] and Van Der Velden [47] showed the controlling influence of injections of posterior lobe extract on the polyuria, and it became accepted in Germany, England and America that the syndrome was the result of hypofunction of the posterior hypophysis.

Meantime in France, Camus and Roussy [5] (1913), following up the work of Aschner [1], initiated the third and present theory of the pathogenesis of the syndrome. They showed that hypophysectomy in itself did not produce a polyuria, but that in those animals which developed the syndrome microscopic examination always revealed a lesion in the floor of the third ventricle. This view was confirmed by Leschke [24], Houssay [19], and Bailey and Bremer [2], who succeeded in producing polyuria by injuring the infundibulo-tuberal region. Richter [32], more recently, has succeeded in producing a permanent polyuria in rats by puncture of the hypothalamus anterior to the tuber cinereum, in the region of the chiasma. The occurrence of diabetes insipidus in encephalitis lethargica, whether in the acute phase or as a sequela, has further emphasized the importance of the hypothalamus in the pathogenesis of the disease.

The pathologist is thus confronted with the remarkable facts that diabetes insipidus is a syndrome produced by a lesion of the anterior hypothalamus, but controllable by injections of posterior hypophyseal extract.

The following three cases were studied in an attempt to correlate these observations :—

Case 1.—The patient was a nurse, aged 30. She gave a history of amenorrhœa for two and a half years. Vision had been blurred for six weeks and for six days before admission there had been a central scotoma of the left eye.

Clinical examination showed moderate progressive acromegaly with bitemporal hemianopsia.

Mr. Dott operated and removed a large pituitary adenoma by the right transfrontal approach. The patient recovered well after the operation but was found to have a post-operative diabetes insipidus. Full vision returned and apart from the polyuria she became perfectly well, and was able to return home. It was possible to control the polyuria by injections of pituitrin—1 c.c. four times per day. Six weeks after her return home patient developed some obscure cerebral catastrophe and was re-admitted unconscious. She died within a few hours.

At post-mortem the adenoma was found to have been almost removed, a small fragment being adherent in the recess at the right of the optic chiasma and about the anterior end of the right optic tract. The cause of death was not clearly ascertained.

Histological examination of the adenoma showed that it was composed very largely of eosinophil cells, the alpha granules staining quite well. The

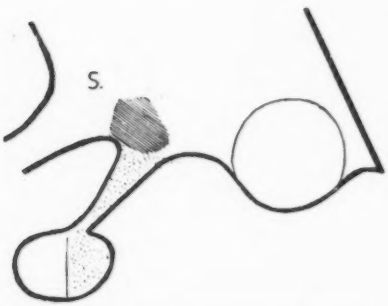

FIG. 1.—Case 1. Diagrammatic representation of area involved by the injury. It will be noted that the fibres coming from the nucleus supra-opticus to the posterior lobe of the hypophysis and the pars tuberalis are interrupted. S = Nucleus supra-opticus.

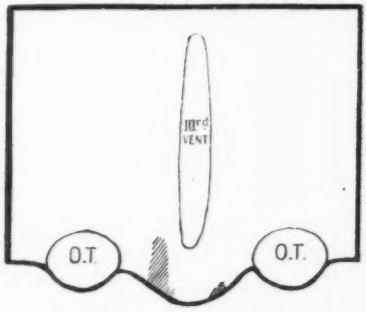

FIG. 2.—Case 1. Diagram illustrating the extent of the lesion on coronal section. The tuberal region has escaped. O.T. = Optic tracts.

adenoma was large and had destroyed the posterior lobe. No pars tuberalis could be found. The hypothalamus showed a small nodule of unremoved adenoma. Small areas of softening were present in this region. Around each area of softening there was a dense astrocytic region, the astrocytes showing sign of division (two nuclei) and having swollen cytoplasm—"gemästete cells." Inside this zone of gliosis were numerous compound granular corpuscles. The areas involved are shown in figs. 1 and 2.

It would seem that these areas represent the result of injury at operation, and as the diabetes insipidus was of post-operative onset it is permissible to regard these as the essential lesions in this case.

Case 2.—The patient was a man, aged 57 years. In 1931 he complained of retro-sternal pain in the left side of the chest. The heart action was satisfactory, though there was occasional irregularity due to extrasystoles. The

PLATE I.

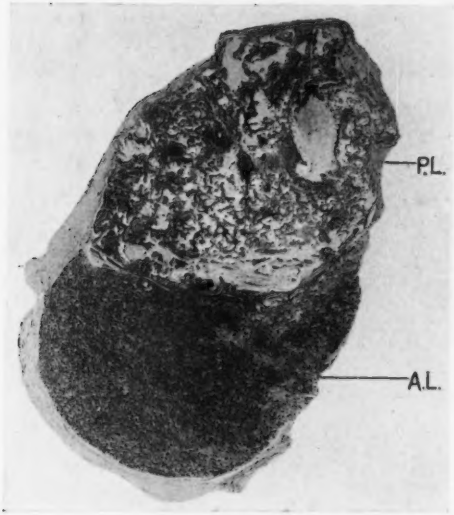

FIG. 3.—Case 2. Section shows the anterior (A.L.) and posterior (P.L.) lobes of the hypophysis. Stained H. and E. Magn. 8 diameters. The posterior lobe is completely occupied by a mucin-secreting papillary adeno-carcinoma. The pars tuberalis is also destroyed.

FIG. 6.—Case 3. Section through upper part of the infundibulum. There is gross infiltration with mononuclear cells. H. and E. Magn. 100 diameters.

To illustrate paper by J. H. Biggart.

blood-pressure some years ago ranged between 150 and 160 mm. Hg., but recently it had been about 115 mm.

In June, 1933, patient began to experience intense and almost continuous thirst, and to pass very large quantities of urine. The urine was of low specific gravity and contained no albumin or sugar. The condition was diagnosed as diabetes insipidus. It was controlled by injections of pituitrin—1 c.c. twice daily.

Two months after the onset of the polyuria the patient began to suffer from headache. This was generalized in character. His doctor noticed some papillœdema of the left eye. This slowly progressed in both eyes. There was also a complaint of tinnitus. The blood Wassermann was strongly positive.

Examination showed a somewhat emaciated man. The cranial nerves were normal with the exception of some papillœdema and a few hæmorrhages in the left retina. Except for a slight degree of arteriosclerosis the general examination was negative. The Wassermann was positive in the cerebrospinal fluid, and the protein showed a definite increase. X-ray showed no deformity of the sella turcica, or clinoid processes.

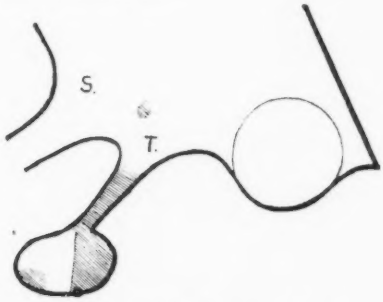

FIG. 4.—Case 2. Diagram to show the site and extent of the metastases. Note that the tuberal region is relatively uninvolved. Fibres from the nucleus supra-opticus to the posterior lobe of the hypophysis are destroyed. S = Nucleus supra-opticus. T = Tuber cinereum.

The clinical opinion was that the patient was suffering from an inflammatory process involving the basal meninges and the tuber cinereum—probably a basal syphilitic meningo-encephalitis with consequent polyuria, fluid obstruction and some degree of hydrocephalus.

A bilateral subtemporal decompression was performed by Mr. N. M. Dott on October 22, 1933.

For two days patient was very well, but on the afternoon of the second day he developed a rigor. After two hours the temperature rose to 102° F., the heart became irregular, and the pulse feeble. Thirty-six hours later he died.

At post-mortem only the brain could be examined. The meninges were thin and translucent. On section of the brain many small jelly-like nodules were found scattered throughout its substance. One such nodule had entirely

replaced the posterior lobe of the hypophysis and the infundibulum. Microscopic studies showed that the small nodules were tumour tissue, the tumour being a mucin-secreting papillary adeno-carcinoma. The whole of the posterior lobe and stalk was found replaced by the growth, and no pars tuberalis could be identified around the upper end of the infundibulum. A small nodule was also present in the tuberal region above the ventral nucleus (Plate I, fig. 3). There was no evidence of a syphilitic basal meningitis. The anterior lobe of the hypophysis showed a small metastasis at its antero-inferior pole. The general distribution of the tumour in the diencephalic region was found by serial section, and is shown in fig. 4. Whilst deposits were numerous in the cerebral cortex, and not infrequent in the cerebellar cortex, there were none in the brain-stem or medulla.

The nature of the tumour suggests that it is a secondary deposit from a tumour of the alimentary tract.

Anatomical diagnosis: Multiple carcinomatous metastases in brain: (?) primary growth in alimentary tract; replacement of posterior hypophysis and infundibulum by tumour; metastasis in hypothalamus.

Case 3.—The patient was a female, aged 54 years. She complained of thirst and polyuria, which had begun seven weeks prior to admission to the Royal Infirmary. The onset of these symptoms was accompanied by headache of a generalized nature. A few days after the onset of the illness the patient had attacks of vomiting which were unrelated to the taking of food. She gradually lost weight.

On examination she was found to be rather drowsy and stupid. The skin was dry, harsh and inelastic. There was an internal strabismus of the left eye. On admission she had Argyll Robertson pupils, but on examination a few days later the pupils were found to react normally. The other cranial nerves were normal, and general examination revealed no abnormality except an inflamed throat. Temperature normal; pulse 90; respirations 20. The urine contained no sugar, albumin or acetone. Its specific gravity was 1,003.

Whilst in hospital the patient was noticed to drink large quantities of fluid and to suffer from polyuria. This was not controlled by injections of pituitrin. A week after admission she developed a temperature and her pulse-rate increased. Her throat became markedly inflamed and she developed a painful inflammation below the angle of the jaw on the left side. She continued in this state for some days and then developed a bronchopneumonia, and died three weeks after admission.

At post-mortem the main findings were marked inflammation of the tonsils and pharynx with involvement of the tissues of the neck, acute splenic tumour, and toxic changes in the liver, kidney and heart. There was congenital absence of the left kidney. The brain showed marked congestion of its surface with small subarachnoid hæmorrhages. The pituitary and infundibulum appeared normal.

On section of the fixed brain there was no gross change except congestion. Histological examination showed an encephalitis affecting the medulla, the

periaqueductal region of the mid-brain, the substantia nigra and the anterior hypothalamus. There was no demyelinization. In the regions affected there was marked perivascular cuffing with lymphocytes and plasma cells, and some destruction of the ganglion cells. The process was most intense in the anterior part of the hypothalamus. In this region the area involved is shown in fig. 5. Apart from a little infiltration of the meninges over the corpora mamillaria the posterior hypothalamus was not involved. In the anterior region the nucleus supraopticus was completely destroyed, and was replaced by an area of intense gliosis, many of the astrocytes having large swollen, rather hyaline cell bodies. The nuclei of the tuber were also destroyed, and in serial sections scarcely a nerve-cell could be found. The inflammatory process extended into the upper part of the infundibulum which was grossly infiltrated with lymphocytes and

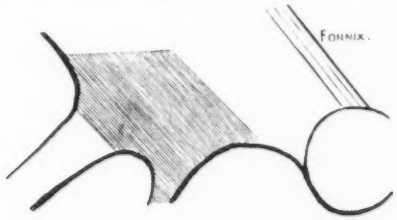

Fig. 5.—Case 3. Diagram to show the area of the hypothalamus involved in the encephalitis. The area includes the nucleus supra-opticus and the nuclei of the tuber cinereum and the upper part of the infundibulum.

plasma cells (Plate I, fig. 6). Some large globoid cells resembling "gemästete" glial cells were found in the stalk. The pars tuberalis was also infiltrated by inflammatory cells, though no degenerative changes could be appreciated in the glandular epithelium. The anterior hypophysis was normal, and the posterior lobe showed no changes. There was no increase in colloid or pigment. The infundibular process of the third ventricle was surrounded by a dense wall of gliosis, in which division of the astrocytes was still taking place.

Anatomical diagnosis: Acute tonsillitis; cellulitis of the neck; acute splenic tumour; toxic changes in all organs; history of diabetes insipidus; acute epidemic encephalitis; involvement of anterior hypothalamus, infundibulum and pars tuberalis.

Discussion.

It will be seen that these three cases, whilst furnishing the same clinical syndrome, have a very varied pathogenesis, one traumatic, one neoplastic, and the third encephalitic. Apart from the cases Lhermitte [25] and others of the French school have traced to a syphilitic basal meningitis involving the hypothalamic region they cover the usual causes of the syndrome of diabetes insipidus. Fink [15], in his analysis of 107 cases, found that 63 per cent. had tumours of the

base of the brain, 13 per cent. had syphilitic processes, 8 per cent. were due to non-specific inflammatory lesions, 5 cases showed tuberculosis, whilst 12 cases were due to trauma. It is probable that these figures give a somewhat erroneous impression, as it would seem from a review of the recent literature that diabetes insipidus is not uncommonly found in epidemic encephalitis.

All these cases have in common a lesion of the hypothalamus, whilst two of them (Cases 1 and 2) have a concomitant lesion of the hypophysis. Before discussing in more detail what nuclei and tracts are involved it is necessary to review the anatomy of this region. Greving [17], Pines [29], and Croll [10] following the earlier work of Cajal [6] and Tello [35], have demonstrated a bundle of unmyelinated fibres which, taking origin in the nucleus supraopticus, is distributed in the posterior lobe of the hypophysis, the supraoptic-hypophyseal tract. According to Cajal some of these fibres end in the pars intermedia, whilst a recurrent branch supplies the pars tuberalis. Other fibres end on the cells of the pars nervosa. It is generally thought that these are efferent fibres. Greving has also shown that the nuclei of the tuber cinereum send their fibres into the mid-brain—tractus tuberalis descendens. The experiments of Beattie, Brow and Long [3] suggest that hypothalamic fibres even enter the spinal cord.

The origin of the secretion of the posterior lobe is still unknown, but wherever it is formed it is probably not in the cells of the pars nervosa, which appears to consist of a rather specialized form of glia, a connective tissue frame-work and blood-vessels. Whether or not the colloid bodies described by Herring [18] and emphasized by Collin [7] and Cushing [9], are the histological evidence of the secretion there is no positive knowledge. The facts are that a biologically active substance can be extracted from the posterior lobe and the tuber cinereum, but that both of these areas are sheathed in an epithelial covering of glandular tissue—the pars intermedia and pars tuberalis—and it is most likely that it is in these glandular areas that the so-called posterior lobe secretion is manufactured. Ablation of the pars nervosa leads eventually to an increase in the "pituitrin" content of the tuber cinereum, but as this is accompanied by a hyperplasia of the pars tuberalis it is still conceivable that the secretion finds its way into the nervous tissue from the epithelial investment (Rubio [33], Trendelenburg [36]). The presence of the secretion in the nervous tissue seems at any rate to indicate the direction of its flow.

In 1930 Popa and Fielding [30] described a peculiar venous return

from the hypophysis. The sinusoids of the glandular portions collect into veins which ascend the stalk, and there break up into capillaries around the nerve-cells of the tuber cinereum. They named this the hypophyseal-portal system. If one is permitted to reason from this anatomical finding it would appear that it represents a mechanism for bringing the secretions of the hypophysis into relationship with the nerve-cells in this region. Whether the path of absorption of the anti-diuretic factor be by this venous circulation, or along the interstitial glial network, appears to be a matter of little note. In either case it will arrive in contact with the nerve-cells of the tuber cinereum and perhaps also with those of the supraoptic and para-ventricular nuclei.

Assessed in the light of these anatomical findings it will be seen that in Case 1 (figs. 1 and 2) the supra-optic-hypophyseal tract is interrupted by the traumatic lesion. The cells of the nucleus tuberis and nucleus supraopticus are largely intact, though some of the cells of the latter nucleus show regressive changes. In Case 2 there is again interruption of this tract without any direct damage to the nuclei. The pars tuberalis is involved in both cases. In Case 3 there is destruction of both groups of nuclei with inflammatory involvement of the pars tuberalis. Clinically Cases 1 and 2 agree in both reacting to injections of the anti-diuretic factor of the posterior hypophysis. Case 3, however, failed to react. The injury of the various structures concerned is shown in Table I.

TABLE I.

	Case 1	Case 2	Case 3
Injury to Supra-optic-hypophyseal tract ..	+	+	+
,, ,, Nucleus tuberis	−	−	+
,, ,, Nucleus supra-opticus ..	Sl.	Sl.	+
,, ,, Pars tuberalis	+	+	Sl.
,, ,, Pars nervosa	+	+	−
,, ,, Pars intermedia	+	−	−
,, ,, Pars anterior	+	Sl.	−
Reaction to Pituitrin	+	+	−

The only anatomical difference of seeming importance is the integrity of the nuclei in Cases 1 and 2, and their absence in Case 3. This difference, however, seems to be of importance in that it points to a central action for the anti-diuretic factor, i.e., this secretion produces its action through one or other of the nuclei which have been destroyed in Case 3. That it is the tuberal nuclei through which this action takes place is rendered probable by the existence of the tractus tuberalis

descendens, and by a consideration of the experimental work of the French school. Such a central action is further rendered probable by Cushing's experiments [9]. It is also supported by the fact that pituitrin will not control the polyuria whilst the patient is asleep (Labbé and Azerad [22]) or under anæsthesia. Cases refractive to pituitrin are also obtained experimentally by tuberal damage (Dreyfus [12]).

Whilst the French school (Gilbert, Villaret and Saint-Girons [16], Rathery [31]) divide diabetes inspidus into two types: (1) of hypophyseal origin, and (2) of nervous origin: it would seem, if this central action of pituitrin is admitted, that the two types can be reconciled.

The following figure is an attempt to explain these varied findings (fig. 7).

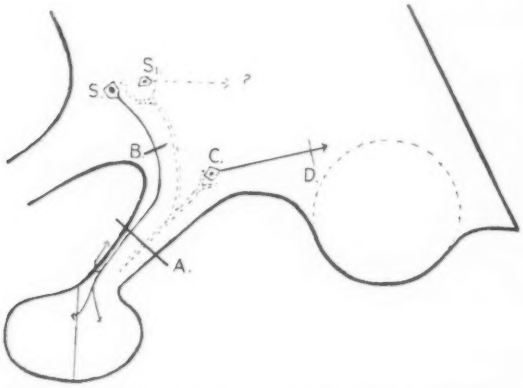

FIG. 7.—Diagram to illustrate the sites of the lesions producing diabetes insipidus (*vide* text). S = Nucleus supra-opticus; S_1 = the tract described by Greving; C = Tuberal nuclei; CD = Tractus tuberalis descendens: A, B, C, D represent possible sites of injury.

A lesion at "A" may produce a polyuria by interruption of the supra-optic-hypophyseal tract. This division would presumably lead to a diminution of the secretion of the anti-diuretic factor, but this would be compensated for by the pars tuberalis which escapes. In fact according to Rubio [33] the pars tuberalis will hypertrophy. A lesion at "B" will cut off the secretory fibres to the whole epithelial investment of the pars nervosa and pars tuberalis, and so lead to the establishment of a permanent diabetes insipidus. Such a case, however, will be controllable by injections of pituitrin as the effector pathway from the nuclei of the tuber cinereum is still intact (Cases 1 and 2). A lesion at C or D, however, which destroys the effector pathway (Case 3), will result in a polyuria which is refractory to treatment. According to Dreyfus

such cases are rare in human pathology, and constitute but 5 per cent. of all cases of diabetes insipidus.

Such a theory would also embrace the experimental polyuria of Bernard and Kahler, and in the case of the permanent polyuria produced by the latter it would be proof of the theory if pituitrin were without effect.

It will be seen that the present explanation of the pathogenesis differs from that of many modern authors in that the lesions are considered paralytic in nature and not irritative. It is difficult to imagine a lesion which will continue merely to irritate over a period of years.

Whether or not complete destruction of the hypophyseal tuberal mechanism would eventually be compensated for by some lower centre remains a matter of conjecture. Newton and Smirk's [28] recent work on decerebrate hypophysectomized cats suggests that such a theory is feasible, and may explain the gradual disappearance of the polyuria in some chronic cases.

Summary.

(1) Three cases of diabetes insipidus are described.

(2) On the basis of these and of the cases recorded in the literature an attempt is made to explain the mechanism by which the disease is produced.

I am indebted to Dr. Dott for the clinical records of Cases 1 and 2, and to Colonel Harvey of the Royal College of Physicians' Laboratory for the specimens. To Dr. Comrie I am indebted for the clinical record of Case 3.

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FAMILIAL DEGENERATION OF THE CEREBELLUM IN ASSOCIATION WITH EPILEPSY.

A Report of Two Cases, one with Pathological Findings.

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The primary cerebellar atrophies have always provided the neuropathologist with material for speculation and a considerable amount of attention has been devoted to the difficult task of separating them into various morphological types; difficult because there are relatively few cases in which the disease is limited to the cerebellum. In fact, it is well known that both the non-familial and the familial instances of this disease have presented manifold combinations of lesions of the cerebellar cortex and its connections in the brain-stem and spinal cord, with the result that numerous gradations exist between Friedreich's spinal ataxia and the cerebellar cortical atrophy of André-Thomas. They represent a heterogeneous group of cerebello-spinal degenerations which Raymond [1] would regard as examples of a premature physiological senescence localized to certain organic systems, and in which the histopathological picture is subject to individual or familial variations.

Certain fairly well defined types, however, can be recognized, and with regard to the so-called acquired cerebellar atrophies, most neurologists are willing to accept the triple division proposed by Marie, Foix and Alajouanine [2], viz.: primary parenchymatous atrophy of the cerebellar cortex (delayed cortical cerebellar atrophy); olivo-ponto-cerebellar atrophy, and olivo-rubro-cerebellar atrophy. From an anatomical standpoint such cases are exceptionally pure, though it is impossible to differentiate them clinically, and several transitional types have been described. Ramsay Hunt [3] has reported a case of primary atrophy of the dentate system in association with Friedreich's disease, and more recently Greenfield [4] described two cases of spino-cerebellar degeneration occurring sporadically in elderly patients.

Unfortunately adequate histopathological studies have been scanty and the number of verified cases of the cortical and olivo-ponto-cerebellar atrophies are scarcely more than twelve of each type, while the

olivo-rubro-cerebellar atrophy is at present limited to one case. Moreover, the olivo-pontine type has shown occasional familial incidence, but the cortical type has not, unless one includes the four cases in one family described by Holmes [5], of which the only one verified showed an olivo-cerebellar atrophy.

It is with these facts in mind that the following report is made upon two epileptic brothers, each of whom developed a cerebellar syndrome in middle life. One of them has recently died from phthisis, thus affording an opportunity of examining his central nervous system, which revealed a pure cortical cerebellar atrophy As far as I have been able to study the literature, this appears to be the first case of familial degeneration in which the atrophy was limited to the cortex. The association with epilepsy is also unusual and deserves special consideration.

The family.—This consists of 12 children, 7 males and 5 females. Six of them are at present alive, and with one exception have all been recently examined by the author.

The father died at the age of 75, and is reported to have been strong and healthy. He was a chronic alcoholic, as was his brother and father, but he worked as an engine driver until 70. The mother, an only child, died at the age of 72, and was not related to the husband (no consanguinity). Her gait was apparently normal. There is, however, a strong history of tuberculosis, and her mother and two uncles died from this disease.

Of the children, No. 1, the eldest, is now 54, and shows no cerebellar symptoms.

No. 2 was killed in a pit accident at the age of 27.

No. 3 is 49 years of age, has not been examined, but is reported to be normal.

No. 4 (Case 1 described later) suffered from epilepsy since infancy; developed a cerebellar syndrome at 41; died of phthisis at 46.

Nos. 5 and 6 were twins and both died when 7 to 8 months old from marasmus.

No. 7 died when one month old from whooping-cough.

No. 8 (Case 2 described later) suffered from epilepsy since 19; developed cerebellar ataxia at 37; living, aged 41, an inmate of the South Yorkshire Mental Hospital.

No. 9, aged 40, shows no abnormality.

No. 10 was killed in the War at the age of 20.

No. 11 is now 37 years of age and must be regarded as a suspicious case. He is not epileptic but exhibits a fine tremor of the facial muscles when talking and his gait shows a slight defect of equilibration. When walking heel to toe he staggers a little and he also admits stumbling in the house, especially when tired. No other abnormality can be found and at present it is impossible to say with certainty that there is a cerebellar defect.

No. 12, aged 32, appears normal.

No further information could be obtained regarding the collateral lines, as apparently they are few and mostly extinct, and there is no history of any relative having suffered from ataxia or epilepsy.

The important features of the family history are the presence of excessive alcoholism on the paternal, and tuberculosis on the maternal, side. No member of the family has suffered from epilepsy with the exception of the two brothers described below.

Case 1.—Fred P., the fourth child of the family, had slight epileptic fits at the age of 3 years, but at 11 he was having definite major epilepsy occurring regularly both by day and night. At the age of 25 he began to show mental symptoms necessitating certification, and was, on June 3, 1913, admitted into the South Yorkshire Mental Hospital. His certificates state that he was violent and excited, threatening his mother and shouting that he was the "prophet of God" and the "Holy Trinity."

He remained in the hospital until his death at the age of 46. His first twelve years of residence were uneventful, and the records state that he was in good physical condition but a typical unstable epileptic, averaging three to six fits per month. At 38 he had an attack of typhoid fever from which he made a good recovery.

He was first noticed to be unsteady on his feet at the age of 41, when he frequently stumbled or fell down in the ward. A physical examination at about this period revealed a definite ataxia of both legs. He was then having three to four typical major fits every month, and his treatment consisted of luminal gr. 3 per diem. He was well nourished, of good physique and no skeletal deformities were noticed. The cardiovascular and respiratory systems presented no abnormality. A neurological examination, however, revealed well-marked inco-ordination of lower limbs. His gait was said to be like that of a drunken man, swaying unsteadily on a wide base. There was no Rombergism. The knee-jerks were present and equal and the plantar reflexes flexor. Normal abdominal reflexes were elicited. The pupils reacted normally to light and there was no nystagmus. Both arms showed definite inco-ordination during the finger-nose test, and his speech was slow, drawling and deliberate.

During the next two years his ataxia gradually increased, and at 43 it was found necessary to keep him more or less in bed. He died from pulmonary tuberculosis in May, 1933, at the age of 46.

Case 2.—Bertram P., the eighth child of the family, has been subjected to a more detailed clinical examination.

He was apparently healthy until the age of 19 when, as a result of his first epileptic fit, he fell off his horse during a gun practice of the Royal Field Artillery. More fits followed and he was discharged from the Army.

During the next thirteen years epilepsy became firmly established and he apparently indulged fairly frequently in alcoholic excesses. He carried on an occupation of groundsman, however, until the age of 33, when signs of mental

instability appeared. He was then admitted into the South Yorkshire Mental Hospital in May, 1925, with a history of violence and excitement, attacking other people and threatening to injure himself. Physical examination revealed no abnormality and his gait was noted to be steady. He remained in the hospital for a period of five months, during which time he had three to four fits per month of both major and minor type. He was discharged and remained at home for the next six years under a more temperate régime.

At the age of 40, however, he became mentally unstable again and was re-admitted, but this time with a marked ataxic gait. Both the patient and his relatives report that he first began to be unsteady on his feet at about the age of 37. He is now 41 years of age, and the following account describes his condition at the present time.

He is of good physique and shows no muscular wasting. His height is 5 ft. 8 in. and his weight 10 st. 7 lb. In his general appearance there are no marked departures from normal and no signs of skeletal deformities, such as scoliosis or pes cavus. There is, however, a slight deformity of the left knee due to an old injury.

No abnormality can be detected in the cardio-vascular or respiratory systems. The blood-pressure is 110 systolic and 85 diastolic. The pulse is normal in rate and volume and there are no signs of arteriosclerosis. The urine shows no albumen or sugar and a blood-count revealed no noteworthy change.

The cerebrospinal fluid is clear, colourless, and not under pressure. The cells number 1 per c.mm.: total protein 0·06 per cent.; globulin slightly increased (Nonne-Apelt one plus); Wassermann negative; colloidal gold 0011221110. The spinal fluid thus shows a slight isolated increase of protein such as may be found in any degenerative condition of the central nervous system.

Neurological examination reveals a well-marked cerebellar symptom-complex as shown by a general disturbance of muscular co-ordination. As he sits in the chair a fine rhythmic tremor of the head is noticed, and there is a similar fine tremor of the hands and fingers as he rests one hand in the other. These static tremors are not constantly present but appear intermittently.

When requested to walk he stands up holding himself rigidly, fixes his eyes on the course to be taken, and with much deliberation and concentration starts off rather cautiously. He walks on a moderately wide base, swaying slightly from side to side and holding the head and trunk stiff and in a position slightly in advance of his lower limbs. His legs move in a stilted manner and his arms, though held stiffly, swing slightly at the shoulders. The hands look awkward owing to an unnatural extension of the fingers. In this manner he manages to walk fairly well, even with his eyes closed, and there is no tendency to deviate to either side of a straight line. But when he has to change direction or turn round, he immediately staggers and almost falls over. It is impossible for him to take more than two or three steps forward heel to toe, but there is no evidence of retro- or anteropulsion. Romberg's test is slightly positive, for

though he can stand fairly still with his eyes open, he sways a little when they are closed.

Special cerebellar tests reveal a marked asynergy of voluntary movements in all four limbs. Such movements are carried out in an awkward and stiff manner, accompanied by a hypertonia of the muscles, an exaggeration of the associative movements, and an excessive display of force. The heel to knee is carried out with fair accuracy, though at first he is inclined to lift the heel high in the air before placing it either a little above or below the knee, but improvement is quickly gained on the second or third attempt. The finger to nose test is also performed with good orientation, both with eyes open and closed. When carried out quickly, however, there is a distinct hypometria, the finger always making an abrupt stop about 2 in. from the nose before being carried to its final destination. This sudden check is not followed by a recoil, and therefore constitutes a true "freinage" reaction (bradyteleokinesis) which the French attribute to a lesion of the cerebellum.

In this patient "freinage" can be elicited in both arms with the eyes open or closed, and when the finger finally rests on the nose there develops a slight unsteadiness or rubbing-in motion (defective fixation). When the test is carried out slowly, a slight intention tremor develops as the finger approaches its objective, but it is carried without a check to its termination only to be followed by the rubbing-in motion. The above phenomena can be equally demonstrated by the finger to finger test.

When asked to hold both arms out horizontally, they sway up and down, but do not deviate outwards. There is a marked dysdiadochokinesis during the pronation-supination test, the movements being slow, irregular and obviously requiring much effort. Manipulative movements of the hands are all performed in an awkward, clumsy manner, his fingers giving the impression of being "all thumbs." He is awkward when using scissors or buttoning up his clothes. When asked to toss a coin in the air he takes a long time to adapt the coin on his fingers, and when, with many facial contortions, he eventually jerks it in the air he is unable to catch it. The finger-thumb test as described by Holmes is carried out with fair success.

Writing is a very laborious procedure. He grips the pen tightly in his right hand and writes slowly without tremor, but with many pauses and occasional spurts, with the result that the letters are irregular, wavy and ragged. His attempt to draw a circle or a square demonstrates his inability to keep his pen on a straight course. The tendency to hypometria is also shown by his attempts to draw a straight line between two dots, for he invariably stops short of the second dot.

Experiments with Bárány's pointing tests give rather indefinite results. There appears to be a tendency to mispoint outwards from below upwards and downwards from without inwards, but both are inconstant and accuracy is quickly obtained. When asked to touch a point 10 in. above the bed with his foot, there is marked overflexion of the limb, and the left leg shows distinct unsteadiness and frequently falls short of the mark. With his eyes closed his attempt at writing a figure 8 in the air with his foot is quite good.

There is no evident hypotonia except perhaps in the arms. It is difficult to get him to relax, but there is a slight flabbiness at the wrist and the Stewart-Holmes rebound phenomenon is occasionally obtained. The muscles become hypertonic on every attempt at movement. Cerebellar catalepsy could not be demonstrated, and there is no apparent decomposition of movements. It is difficult for him to sit up from a dorsal position, and in doing so he raises both legs high above the bed. There is no paralysis or paresis of any muscle groups.

Speech is slow, monotonous, deliberate and characterized by frequent long pauses. He gives the impression that considerable effort is required to formulate his words, although he is able to shout.

All cranial nerves are normal. The pupils are equal, regular, and react well to light and accommodation. Ocular movements are normal in range and there is no nystagmus. A rough test of the visual fields shows no abnormality, and the fundi are normal. No vestibular defect could be found when using the caloric test.

The abdominal reflexes are diminished, but a definite contraction can be obtained in the umbilical region on both sides. A heavy blow is required in order to elicit the knee-jerks, but they are present, equal, and not pendular. The ankle and arm jerks are obtained with difficulty, and the plantar reflexes are both flexor.

No disturbance can be found in the sensory system—touch, pain, thermal, joint and stereognostic tests all giving normal results.

We may say, therefore, that this patient exhibits a profound general disturbance of all purposive movements, as shown by muscular inco-ordination and asynergy. Furthermore, there is a hypotonia during repose (arms) and a marked hypotonia during muscular action.

It is evident also that the cerebellar defect is to a great extent compensated by cerebral control and correction, for his every movement appears to require constant voluntary attention and effort. In fact, when cerebral influences are diminished or abolished, as frequently occurs during the temporary confusion following an epileptic fit, he is then unable to stand, and has been seen to spin round like a top.

Epileptic fits have been occurring regularly since admission with a frequency of four to six per month. They are typical epileptiform seizures of the grand-mal type and show tonic and clonic stages. No evidence of an aura can be elicited, and there is no opisthotonos suggesting the so-called cerebellar fit. He has several scars on his head from falling during fits. Myoclonic spasms are infrequent, but they have been observed occasionally, especially during sleep. He bites his tongue and frequently has involuntary micturition. His treatment has been luminal 3 gr. every night.

Mentally he is rather apathetic and lacking in concentration. His memory is slightly impaired, but his general intelligence seems fair. He is quarrelsome, impulsive and quick tempered, but shows no delusions.

Pathological Examination of Case 1.

The autopsy was carried out three and a half hours after death, and, apart from general emaciation, the external examination revealed no notable abnormalities. The left pleural sac was thickened and contained pus. The left lung exhibited an advanced stage of chronic ulcerative phthisis limited to the upper lobe, and there was an apical fibro-caseous lesion in the right lung. The heart was small and the left ventricle dilated. The myocardium was soft and flabby. There was no atheroma in the aorta. The liver presented a nutmeg appearance due to chronic venous congestion. The spleen appeared normal. Both kidneys showed evidences of chronic intestinal nephritis, the capsule being slightly thickened and adherent.

Fig. 1.—Upper surface of cerebellum, showing atrophy of the folia and widening of the sulci.

The skull-cap was normal in size and thickness and the dura mater healthy. The whole brain before section weighed 1,280 grm. The pia-arachnoid appeared slightly thickened over the vertex, but it stripped easily and without decortication. The external appearance of the cerebrum was normal apart from slight generalized atrophy of the convolutions. There was no abnormality of the circle of Willis and no appreciable arteriosclerosis. The lateral ventricles were slightly dilated, but the ependyma was healthy. The weight of the cerebrum was 1,120 grm.

The cerebellum was obviously smaller than normal, and showed marked atrophy. The weight of the brain-stem and cerebellum was 130 grm. instead of the normal 170 grm. The loss in weight of the

FIG. 2.—Sagittal section in the median plane of the vermis of (above) Case 1, showing atrophy of the folia, especially marked in the culmen and clivus; and (below) an epileptic, aged 32, with approximately the same weight cerebrum. Both were photographed with the same magnification for comparison.

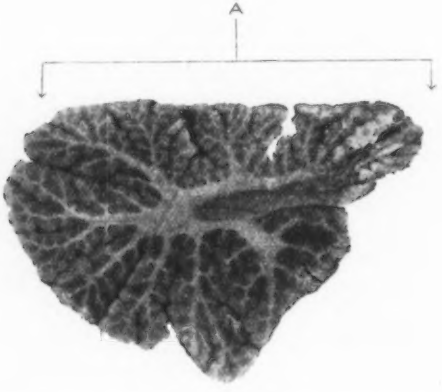

FIG. 3.—Sagittal section through the centre of the right cerebellar hemisphere, showing marked atrophy of the superior surface at A.

cerebellum may therefore be considered as approximately one-quarter. Although the cerebellum showed a general reduction in size, on closer examination it was evident that the atrophy was more marked on the anterior and superior surfaces, particularly in the superior vermis, semilunar and quadrilateral lobules, and owing to the disappearance of the normal ridge-like elevation of the superior vermis (monticulus cerebelli) the upper surface of the cerebellum was quite flat and the folia appeared shrunken and widely separated (fig. 1). On the anterior surface, there was a marked exposure of the middle peduncles as a result of the shrinkage of the folia round the great horizontal fissure. The inferior surface, on the other hand, presented a more or less normal contour, although the folia were smaller than normal (fig. 2). Palpation of the cerebellum revealed a normal consistency. The meninges appeared healthy.

FIG. 4. – Weigert-Pal preparation of upper dorsal region of the spinal cord, showing an asymmetry of the two halves due to a deepening of the postero-lateral groove on one side. Note the distortion of the posterior root.

Sagittal sections through the vermis and lateral hemispheres further demonstrated the generalized atrophy, but with focal emphasis almost sharply limited to the folia of the upper surface of the organ (figs. 2 and 3).

The pons, medulla, and cervical cord were normal in size and shape. The dorsal region of the cord, however, was abnormally slender and presented a peculiar ribbed appearance due to a deepening of the postero-lateral grooves (fig. 4). Sections of this region of the cord showed an asymmetry due to the postero-lateral groove on one side being deeper than the other, with consequent shortening and widening of the posterior root. The lumbar region of the cord was normal in size and shape.

Histological examination.—The brain and spinal cord were fixed in formalin and pieces taken from various levels for staining by the following methods: Toluidin blue for Nissl granules; Victoria blue for fibrillar neuroglia; Bielschowsky's silver method for neurofibrils; Hæmatoxylin and scharlach R.; Weigert-Pal and Marchi methods for myelin sheaths.

Cerebellum.—Nissl sections of the superior vermis and quadrilateral lobes showed an almost complete destruction of the cells of Purkinje, a marked narrowing of the molecular layer, and a thinning of the granular layer (Plate II, fig. 5). Normal Purkinje cells could not be found in any of the sections from the upper surface of the cerebellum, for those that remained were in advanced stages of disintegration (fig. 6). In this region, the majority of the folia were absolutely devoid of Purkinje cells, but here and there one found a folium containing a few disintegrating forms, and in the latter there was a less severe affection of the molecular and granular layers.

The absence of the Purkinje cells produced a clear unstained zone giving the appearance of superficial cleavage of the outer border of the granular layer. At the junction of the molecular and granular layers, especially at the free borders of the atrophic folia, there was frequently a definite band of irregular dark-staining neuroglia nuclei (Bergmann's glial cells).

The depth of the molecular layer was reduced by a half to a third over the crests of the folia, and in some parts there was an obvious sub-pial belt of neuroglial fibres. The outer third of this layer showed a status spongiosus, and there were frequent accumulations of corpora amylacea.

The granular layer showed a marked rarefaction in addition to a reduction in depth. There was a definite loss of granule cells and a disappearance of their normal cluster arrangement. The white centres of the folia appeared normal (figs. 5 and 6).

In sections of the inferior surface of the cerebellum, there was a less severe affection of the cortex. Here the main incidence of the disease appeared to fall on the Purkinje cell layer, the molecular and granular layers presenting an almost normal appearance. The Purkinje cells were frequently normal in number but many exhibited varying degrees of degeneration from a mild chromatolysis to pale shadow forms. In several parts, however, there were large gaps in the line of cells.

Anderson's Victoria Blue method showed very little gliosis apart from slight thickening of the radial fibres of Bergmann in the molecular layer, and a narrow band of sub-pial felting at the free borders of the atrophic folia.

With Bielschowsky's method, the atrophic folia showed a crowding of the fibrils, many of which appeared to be abnormally thickened. The horizontal and radial fibrils of the molecular layer and the fibrils of the granular layer were well shown, and apparently not much reduced. The

PLATE II.

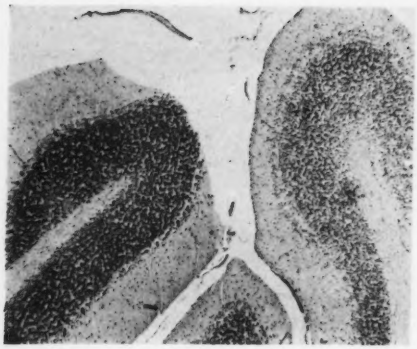

FIG. 5.

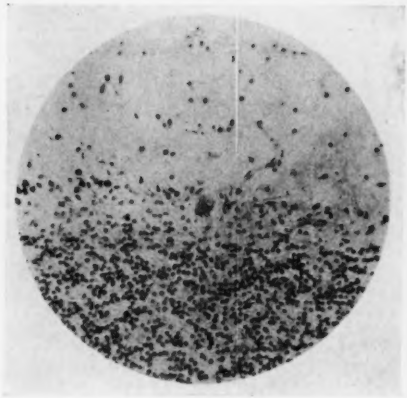

FIG. 6.

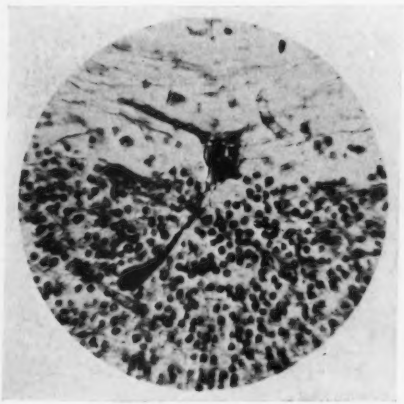

FIG. 7.

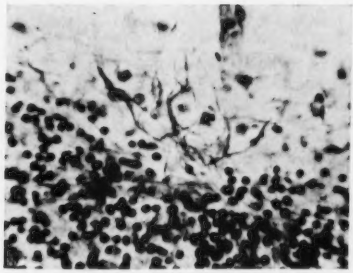

FIG. 8.

FIG. 5.—Nissl section of the superior vermis at the bottom of the sulcus post-centralis. The folium on the right is part of the culmen and shows marked atrophy of the molecular and granular layers, and disappearance of the Purkinje cells, leaving a clear zone. The folium on the left is part of the lobus centralis, and is relatively normal, but it contains only a few degenerating Purkinje cells.

FIG. 6.—Nissl section of the crest of an atrophied folium showing a belt of irregular dark-staining neuroglial nuclei in the intermediate layer. In the centre is a disintegrating Purkinje cell.

FIG. 7.—Bielschowsky preparation showing a "torpedo" or spindle-shaped swelling on the axon of a Purkinje cell.

FIG. 8.—Section of the cerebellar cortex stained by Bielschowsky's method, showing the preservation of the basket fibres and absence of Purkinje cells.

To illustrate paper by Frederick T. Thorpe.

basket fibres were also in many places well preserved, even in the most atrophic regions (fig. 8). In sections from the upper surface of the cerebellum the few remaining Purkinje cells presented a large fusiform swelling on their axons situated a short distance from the base of the cell, and in the outer third of the granular layer (fig. 7). These spindle-shaped swellings have been described by Bouman as torpedoes or "Axonschwellungen." They are almost as large as the Purkinje cell and are impregnated homogeneously with silver stain, although small vacuoles could occasionally be seen.

Sections of the upper surface stained by Weigert-Pal method revealed a distinct loss of myelinated fibres in the central white matter of the atrophic folia. The meninges and blood-vessels everywhere presented a normal appearance and no sign of an inflammatory reaction could be found. The central white substance of the hemispheres shared in the general reduction in size, with the result that there was an apparent overcrowding of nuclei, but no appreciable gliosis could be found in the Victoria Blue sections.

The cells of the corpus dentatus and roof nuclei were normal in number and size, but in the Nissl preparations the ganglion cells were pale and frequently showed an increase of lipofuchsin granules and an eccentricity of the nucleus. There was an increase of neuroglial nuclei between the ganglion cells of the dentate nuclei but no loss of fibres could be detected in the Weigert-Pal sections.

Brain-stem.—In this region very little abnormality could be detected, although sections were taken from various levels and stained by Weigert-Pal and Nissl's methods. No evidence of tract degeneration was found in the cerebellar peduncles or in the pyramidal fibres. The nerve-cells of the red nucleus, nuclei pontis and motor nuclei of the medulla all appeared healthy. The cells of the inferior and accessory olives were normal in number and size, but their cytoplasm showed no Nissl's granules and stained darkly and homogeneously, although the nuclei and nucleoli were well preserved. There was no excess of neuroglial nuclei between the nerve-cells of the olives.

Spinal cord.– Weigert-Pal, Marchi, and Nissl preparations were made from the cervical, dorsal and lumbar regions of the spinal cord. No tract degeneration could be found, and no loss of myelinated fibres in either the pyramidal or spino-cerebellar tracts. The anterior and lateral horn cells at all levels appeared normal or showed only slight chromolytic changes. The cells of Clarke's column were not reduced in number but showed marked chromatolysis. Throughout the grey

column the blood-vessels appeared engorged, while here and there small capillary hæmorrhages could be seen. The spinal meninges showed no abnormality, nor could any inflammatory reaction be detected.

In all sections of the dorsal region of the cord there was a marked deepening of the postero-lateral groove on one side, at the bottom of which the posterior root appeared broadened and distorted. This produced a peculiar asymmetry of the two halves.

Cerebrum.—Nissl sections of the prefrontal lobes, the hippocampus and basal ganglia showed no abnormality. In sections of the motor cortex, however, the majority of the Betz cells were undergoing chromolytic changes and many had been reduced to pale shadow forms.

Summary.—To sum up, we have in this family of twelve members two brothers who were afflicted with the same symptoms, viz.: A typical idiopathic epilepsy followed, after a period of some years, by a gradual development of a pure cerebellar syndrome characterized by an ataxic gait, inco-ordination of movements in the upper limbs, and a slow, drawling speech.

In the case of the elder brother, epilepsy began at the age of 3, and the cerebellar symptoms at 41, but in the case of the younger brother epilepsy did not appear until the age of 19, yet the cerebellar symptoms developed at 37. There is, therefore, a marked difference in the length of time between the onset of epilepsy and the manifestations of cerebellar dysfunction in these two cases; viz., thirty-eight years in one, and eighteen years in the other.

It is difficult to decide with certainty the order in which the cerebellar symptoms appeared, as in both patients the upper and lower limbs were equally affected at the time of examination. The disturbance of gait would naturally attract more attention, and in both patients it was the first symptom to be observed.

There was no nystagmus, and no motor paralysis or sensory disturbance. The tendon reflexes were unaffected and there was no disorder of the sphincter function. Both patients presented mental disturbances which were established long before the onset of cerebellar symptoms, and were no doubt dependent upon the epilepsy.

The additional features of interest observed in the second case consisted of static tremors of the head and limbs, hypertonia during movement, and a hypometria of the upper limbs producing a typical freinage reaction.

The anatomical basis of these cerebellar symptoms was found at the autopsy of the first case to be a degenerative affection of the cerebellar

cortex, and it is reasonable to assume that the same condition exists in the cerebellum of the brother now living. In the former, the duration of the cerebellar syndrome was approximately five years, when the patient died from phthisis, and the cerebellum was found to be reduced in size, and to have lost about one-quarter by weight. The folia were shrunken and atrophic, especially on the upper surface of the organ, including the superior vermis, quadrilateral and semilunar lobules.

Histologically the essential change appeared to be a primary degeneration of the Purkinje cells, starting in the laminæ of the superior surface and gradually spreading to those of the lower surface. The basket fibres were very little affected. The narrowing of the molecular layer, the rarefaction of the granular layer and the shrinkage of the white matter were apparently secondary to the disappearance of the Purkinje cells and fibres, for in the most atrophic folia all three cortical layers were equally affected, whereas in the least atrophied folia of the inferior surface the pathological process was limited to the Purkinje cells. The blood-vessels and meninges were normal.

The increase of pigment in the cells of the corpus dentatus cannot be regarded as important because such changes are common in advancing age and in this particular case there is the additional factor of the terminal toxæmia. There were no tract degenerations in either the brain-stem or spinal cord, and the mild chromolytic changes found in the cells of the inferior olives and other nuclei were in all probability due to the terminal condition. No changes of note were found in cerebral cortex and basal ganglia, apart from chromatolysis and commencing disintegration of many of the Betz cells. The asymmetry and smallness of the dorsal region of the spinal cord must be regarded as a developmental defect.

Discussion.

The cerebellar syndrome.—The cerebellar lesion in the above cases may be truly described as a chronic parenchymatous degeneration of the cortex and it in no way differs from the sporadic cases which Marie, Foix and Alajouanine have called the delayed cerebellar atrophies. The predominance of the atrophy in the superior face of the organ, which was so well marked in my case, is characteristic of the whole group, and roughly corresponds to Edinger's conception of the palæo-cerebellum. Mathieu and Bertrand [6] point out that the vermis usually appears more atrophied than the lateral lobes, and suggest that this is due to the longer folia and deeper sulci of the former. The axon-swellings

of the Purkinje cells are also a constant finding and would appear to indicate an early lesion of these cells. They have been well described by Bouman [7] who found them in cases of senile dementia, amaurotic family idiocy, juvenile paralysis, and Huntington's chorea. He regards them as identical with the local swellings of the neurons found by Cajal in injuries to the cerebellar cortex.

Primary parenchymatous degeneration of the cerebellar cortex is at present limited to twelve cases and these have been recently reviewed by Parker and Kernohan [8]. They were all of the non-familial type and as far as I have been able to study the literature the two cases described above appear to be the first familial cases in which the lesion is confined to the cerebellar cortex.

Holmes, however, has described four cases of cerebellar degeneration in one family, but a pathological study of one of them revealed, in addition to a typical cortical affection, a sclerosis of the inferior olives. This case has therefore been called olivo-cerebellar atrophy, although Holmes considered the olivary lesions to be secondary to that of the Purkinje cells. All four cases were very similar to mine, and there appears to be very little justification for separating them into two groups. The olivary lesion in Holmes' case could be explained by the long duration of the cerebellar symptoms, viz. 35 years, as compared with five years in my case. On the other hand, Van Bogaert and Bertrand [9] hold that the Purkinje cell degeneration is frequently a trans-synaptic extension and not necessary to the degeneration of the cerebello-petal fibres, as has been shown by cases of olivo-pontine atrophy in which the cortex is not affected. Marie, Foix and Alajouanine also regard the pure atrophies of the cerebellar cortex as separate and independent affections.

From a clinical standpoint, the cases of familial degeneration of the cerebellum differ from the sporadic forms only in their tendency to appear at an earlier age. In the twelve sporadic cases reviewed by Parker and Kernohan, the average age of onset was 62, whereas in the two cases described above the onset was at 41 and 37. In Holmes' four familial cases the onset was at 36, 38, 35 and 35 respectively, while Stone [10] has recently published a clinical report (not verified by post-mortem) of two typical cases affected at $33\frac{1}{2}$ and 37, whose father and great-uncle in the first case and paternal uncle in the second case, were similarly affected at 36, 37, and 34, respectively.

The familial forms would thus appear to occur with great regularity in the fourth decade with an average age of onset at 37.

The clinical manifestations are essentially similar in the whole group of cases, viz. a gradual and insidious onset of muscular inco-ordination, involving the body symmetrically, progressing steadily and slowly over a number of years to helplessness and death from intercurrent disease. In the majority of cases the lower limbs were affected before the upper and speech became monotonous and drawling. Nystagmus is unusual but in some cases there have been nystagmoid jerks on lateral deviation of the eyes. Hypotonia is also rarely prominent, and its absence has been attributed to the slow development of the disease and the consequent influence of cerebral compensation.

In the second case described above, all voluntary movements were accompanied by a hypertonia, a phenomenon which has been observed in several of the published cases. R. Brun [11] offers an explanation of this when he states that the cerebellum may possess at the same time tonic centres and inhibitory centres working in equilibrium, the dentate and roof nuclei (tonic centres) being under the inhibitory influence of the lobes and vermis. Lesions of the dentate nucleus and superior peduncles would therefore cause hypotonia and lesions of the afferent system and cortex, hypertonia.

The olivo-ponto-cerebellar type of atrophy has already shown occational familial incidence, and it is evident that the same may be said of the pure cortical type. In fact, both conditions may be inherited as a Mendelian recessive in a manner similar to that of Friedreich's disease, which also frequently occurs in a non-familial form. There appears to be in these cases an inherited endogenous tendency to early degeneration (abiotrophy) of the cerebellar system of neurones. Such a tendency may be limited to an individual or it may occur in familial form. In the former case, it has been suggested by Marie, Foix and Alajouanine that the degeneration may be produced or precipitated by an exogenous infection, but such a history is by no means constant, and the evidence rather unconvincing.

The close association between cerebellar atrophy and Friedreich's disease is borne out by the presence of a slender and asymmetrical cord in the first patient. Similar developmental defects are not infrequently found in Friedreich's disease.

The Relationship between Cerebellar Atrophy and Epilepsy.

The two cases of cerebellar atrophy described above are somewhat unique in the fact that they were the only two members of the family

suffering from epilepsy. At first sight it might appear that the cerebellar atrophy was in some way specially connected with the occurrence of epileptic fits. There is, indeed, abundant evidence to show that epileptic fits frequently produce degenerative changes in the cerebellar cortex.

Spielmeyer [12] has devoted much attention to this question, and has discovered characteristic cell degenerations in the cornu ammonis and cerebellum in as many as 80 per cent. of epileptic brains. He regards the changes in the cerebellum as similar in principle and also as frequent as those of Ammon's horn. These consist of scleroses—a proliferation of the neuroglia in the molecular layer, which replaces the degenerated nervous tissue substance and, above all, the loss of Purkinje cells. He also suggests that these changes are related to the mechanical factor responsible for the seizures; i.e., they are ischæmic changes resulting from angiospastic constriction. Spielmeyer believes that the cornu ammonis and the Purkinje cell layer of the cerebellum have a relatively unsatisfactory local blood supply, and are therefore peculiarly sensitive to any partial hindrance to the circulation. In this respect Uchimura [13] has demonstrated that vessels in these areas are unusually long and tortuous, and that the capillary network is less abundant than in other parts of the brain.

It would appear, therefore, that secondary degenerative changes in the cerebellar cortex are a common occurrence in idiopathic epilepsy. But such changes consist of focal areas of atrophy and sclerosis, and are rarely severe enough to produce clinical symptoms. They are of a different order to the widespread diffuse and symmetrical atrophy found in the group of primary degenerations of the cerebellum, of which the case above described is a typical example.

On the other hand, degenerative lesions of the cerebellum with clinical manifestations have been found in cases of myoclonus epilepsy. Such cases have been recorded by Haenel-Bielschowsky [14] and Ramsay Hunt. The latter author reports four sporadic cases of epilepsy and myoclonus which also showed signs of cerebellar dysfunction, consisting of generalized intention tremors, scanning speech, dysmetria, dysdiadochokinesia, hypotonia and asthenia. Unfortunately the anatomical basis of their cerebellar symptoms could not be ascertained, but a histological study of a similar case associated with Friedreich's disease suggested that a "primary atrophy of the dentate system" was responsible.

It is evident, therefore, that primary cerebellar atrophy occasionally

occurs in subjects of myoclonus and epilepsy. In the two cases I have described there was a long-standing epilepsy, but no myoclonus. The epilepsy and cerebellar symptoms may be considered as manifestations of two distinct disorders in the same individual, for, as pointed out by Ramsay Hunt, combined forms of the various congenital, familial and hereditary types of nervous disease are by no means uncommon. Many such instances have been described by Jendrassik [15]. The combination of epilepsy and Friedreich's disease excites little comment, but in view of Spielmeyer's researches the occurrence of a cortical cerebellar atrophy in an epileptic is of special interest and suggests the possibility of a closer pathological association between these two conditions.

RÉSUMÉ.

A familial form of primary parenchymatous atrophy of the cerebellar cortex is described, in which two brothers, at the ages of 41 and 37 respectively, developed a progressive ataxia of legs and arms, and a slow drawling speech. The anatomical basis of these symptoms was ascertained in one of them after a duration of five years, and was found to be a pure cortical type of cerebellar atrophy. The cerebellum was reduced in size by approximately one quarter, and showed a generalized symmetrical atrophy with marked emphasis on the upper and anterior surface, especially the superior vermis and quadrilateral lobes. Histologically, the essential lesion was a diffuse destruction of the cells of Purkinje. This particular type of atrophy has heretofore only been described in non-familial cases, unless one includes the Holmes family of four cases, of which the only one examined histologically revealed an olivo-cerebellar atrophy.

Familial degeneration of the cerebellum occurs more often in males, and the onset is between the ages of 32 and 41, whereas non-familial forms tend to occur at a much later age. Both forms are assumed to be due to an endogenous degenerative process or abiotrophy, but in the sporadic cases there may be an additional exogenous infective or toxic factor.

The frequent combination of cerebellar atrophy and lesions of the spinal cord is mentioned, and in the case described a developmental defect of the cord was found, which suggests a latent association with Friedreich's disease.

The two patients described were subject to epileptic seizures which had been present for thirty-eight and eighteen years before the onset of cerebellar ataxia. The cerebellar lesion, however, was not the focal

ischæmic type which Spielmeyer finds in most epileptic brains, but a gross generalized atrophy typical of the primary degenerations.

The association of cerebellar atrophy and epilepsy in these two cases is regarded as accidental, and merely represents the not uncommon occurrence of a predisposition to two independent nervous disorders in one individual.

I wish to express my thanks to Professor A. J. Hall for his helpful advice and criticism; and to Dr. Arthur Pool, the Medical Superintendent of the South Yorkshire Mental Hospital, for permission to publish these cases.

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THE FRONTAL LOBE IN MAN: A CLINICAL STUDY OF MAXIMUM REMOVALS.[1]

BY WILDER PENFIELD AND JOSEPH EVANS,
Montreal.

REMOVAL of very large areas of the human brain in neurosurgical practice offers an opportunity for detailed neurological study, especially in the occasional case which fortuitously presents many of the conditions which would be demanded of a physiological experiment. Three cases of radical removal of large portions of one frontal lobe have been selected for this communication because of unusual opportunity for study before and after operation and because the excised portions of the brain could be accurately examined.

Advance in knowledge of the functions of the frontal lobes is difficult to secure because of the fact that substitution of one cerebral region for another is no doubt possible, and there may well be bilateral representation of many cerebral processes which take place in this *terra incognita*. Furthermore, animal experimentation can contribute little, as all animals, even the anthropoids, possess but rudimentary prefrontal development and it is impossible to explore the finer thought processes of speechless animals.

Extirpation of a tumour, however radically carried out, does not provide a perfectly satisfactory subject for study, as tumours often displace cerebral tissue to a great extent without destroying the tissue or its function. The only tumour cases which are acceptable for investigation are those in which an infiltrating neoplasm has made it advisable to resect a large block including brain and tumour. The cases, however, which are most useful for our present purpose are those of patients suffering from chronic epilepsy due to a focal lesion of such a type and situation that lobe amputation offers the only hope of relief from the seizures.

Case 1.—R. I., R.V.H. Right frontal extirpation; calcified oligodendroglioma.

This case offers an unusual opportunity in that the patient was observed closely from childhood onward and the removal was radical. The patient was

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43 years of age. Occasional "splitting" headaches began at the age of 14. At the age of 20 there was a Jacksonian seizure. This was followed by a series of such seizures at 28 years of age and another at 33, at 34 and at 40 years. From 40 to 43 years of age, when operation was carried out, there were occasional small Jacksonian attacks.

Dr. Colin Russel, who examined her for us on her arrival in Montreal in November, 1928, found bilateral papillœdema, left plantar extension, comparative weakness of the left arm and leg, and he made the observation that she was "mentally not up to her own standard in looking after household arrangements."

A right frontal osteoplastic craniotomy was carried out by one of us (W. P.)

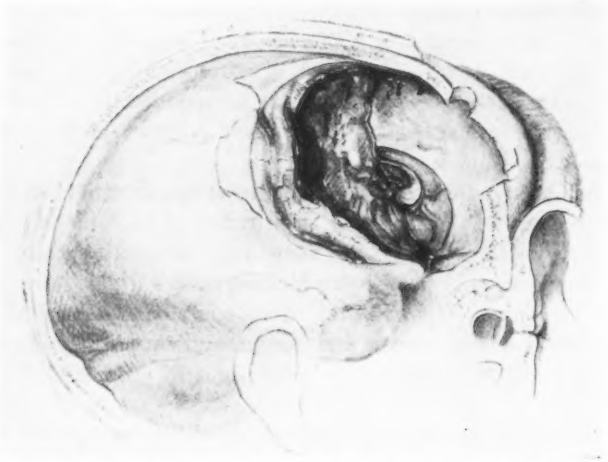

FIG. 1.—Operative sketch showing the extent of the removal in Case 1. This is the unprompted conception of the artist who was present at the operation.

and a large, partially calcified oligodendroglioma was exposed. It infiltrated the frontal lobe but did not involve the anterior pole. Tumour and lobe, except for precentral gyrus, were resected *en bloc*. Fig. 1 indicates the extent of removal as it appeared to the artist who was present at operation.

It is always difficult when dealing with an expanding lesion to know how much the cerebral tissue has been rarefied and displaced without being rendered functionless. Therefore we have indicated in fig. 2 our conception of the site of removal by the continuous line to which the arrows point. An infiltrating tumour does not displace brain to the same extent that a slowly growing encapsulated one does, but it does displace it somewhat so that the line of crosses in the same figure gives an estimate of the cerebral tissue actually destroyed which is safely conservative.

The operation was carried out under local anæsthesia. She may have lost

consciousness for a short time when there was a sharp hæmorrhage, but she was otherwise alert during the procedure, spoke to the operator frequently and talked intelligently about her children, her chief preoccupation. At the end of six hours of this operative ordeal she apologized for having made so much trouble!

That night she slept at long intervals. Twice during convalescence she was catheterized, but otherwise recovery was entirely uneventful and she was out of bed in two weeks. Neurological examination on discharge was entirely negative although she was not subjected to so searching a sensory examination as the next case. Two months after operation she had returned to her own family and during the year which followed lived a happy and essentially normal life as will be described in the discussion to follow.

FIG. 2.—*Case* 1. The solid line indicates the line of removal; the crosses indicate a more conservative estimate of the cerebral tissue actually removed if the displacement which the tumour may have produced be considered.

My instinctive reaction (W.P.) was to withhold this case from publication. The patient was my only sister. But the close bond of sympathy that had existed between us for many years makes it possible for me to evaluate the effect of the loss of the frontal lobe upon her personality and her mental capacity. My opinion at all events must be interpreted in the light of this personal relationship and if she were alive I am sure she would approve of such an analysis in the hope that it might help others.

After this case had been presented before the Association for Research in Nervous and Mental Disease the following letter was received from Professor Russel, which is now printed in full as it expresses his opinion of the case.

"Because of my great interest in her I would have liked to contribute to he discussion of the condition of your sister following lobectomy. You will

remember that I sat and talked to her during the operation and left her only at about 5 o'clock when you were cleaning up. You showed me how much of the anterior lobe had been removed, and one could see in the midline the falx perfectly clean.

"I dropped in to see her between 8 and 8.30 that evening and although she was somewhat nauseated and had been vomiting, probably the result of the local anæsthetic, she expressed her appreciation of what she considered my kindness in giving up my time, so perfectly and with so much courtesy that it was really very impressive. She said that she had felt so afraid of causing you distress by making an exhibition of herself and that I had helped her.

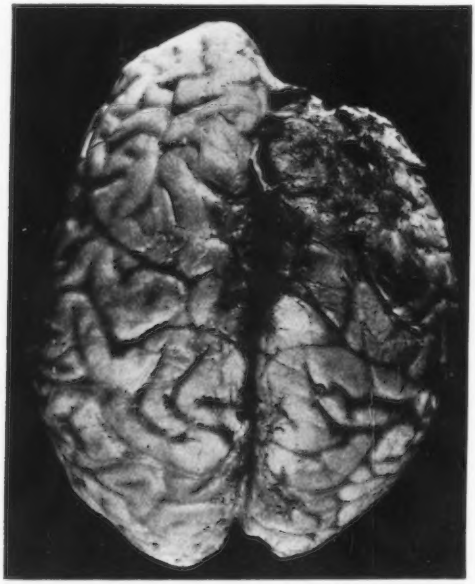

FIG. 3.—The brain of Case 1 as seen at autopsy, two years and five months after the operation of figs. 1 and 2. The anterior portion of the amputated pole is recurrent neoplasm.

When I remarked that the only exhibition I had seen was one of the best exhibitions of courage that it had been my fortune to witness, she expressed her gratitude so nicely that one could not help wondering how much the frontal lobe had to do with the higher association processes. Of course, as you have already said, it is not so much the frontal lobe as a slow growing tumour that involved the frontal lobe, and probably the function of that lobe had been gradually taken on by other parts of the brain.

"During her convalescence I so often would get her to discuss books that she had read, and her memory was so good, and she showed such good judgment in her criticisms that I cannot help but feel that her feeling of

inadequacy explained in her letter to you when she asked for some means of sharpening up her intelligence might very well be explained by the fact that she had been a very conscientious mother of several children who had neglected her social contacts on account of her domestic duties, and was feeling the lack of facility in social intercourse. It is not an uncommon experience under such circumstances."

Her condition following operation will be taken up in detail in the discussion to follow.

FIG. 4.—The same brain as fig. 3, seen from below.

Twenty-two months later, following a rather sudden reappearance of symptoms, she was re-operated upon at our request by Dr. Harvey Cushing who found a recurrence of the tumour and removed it again without any further amputation of cerebral tissue. She continued to feel well but six months later died from hæmorrhage into the tumour and autopsy again showed neoplastic recurrence. Thanks to the kindness of Dr. Carl Rand of Los Angeles, who performed an autopsy, we can show a photograph of her brain (figs. 3 and 4). It will be seen in fig. 3 that there is sufficient regrowth of the tumour to make the hemisphere appear about 3 to 5 cm. longer than it really was. Re-growth of such a tumour not infrequently simulates brain in form.

Complete examination of the brain showed that there was no neoplasm nor abnormality elsewhere. The case will be taken up again under the heading of general discussion.

Case 2.—W. B., R.V.H. Left frontal lobectomy. Post-traumatic epilepsy, cerebral cicatrix.

At 16 years of age he fell from a scaffolding and received a depressed fracture of the right frontal region. He was unconscious for two and one-half weeks. He left the hospital in two months and felt "all right" except that his memory did not seem as good as formerly. He did not work for a year, at the end of which time he took a position as caretaker of a skating rink, a position he continued to hold until recently. At the age of 22, epileptiform seizures of the frontal lobe type made their appearance as described elsewhere.[1]

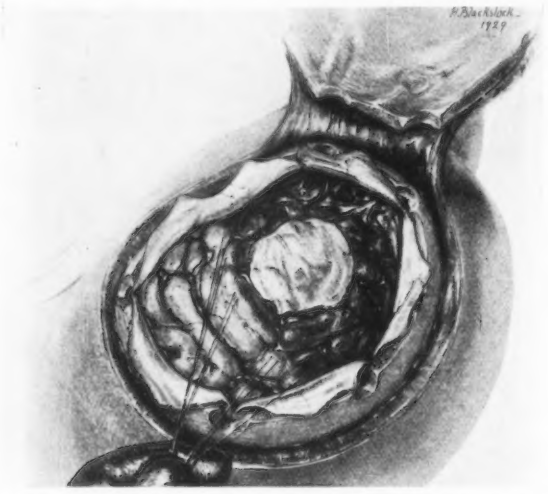

FIG. 5.—Sketch of the lesion exposed at operation in Case 2, showing the sclerosed and atrophic frontal pole and the meningeal adhesions.

Two years later encephalography demonstrated enlargement of the anterior horn of the left lateral ventricle, a cyst in the left frontal lobe and migration of the third ventricle toward that side. Osteoplastic craniotomy was carried out (November, 1929). It revealed abnormal, leathery frontal convolutions and dense dural adhesions (fig. 5). Amputation was carried out through normal tissue as indicated by the cutting threads in fig. 5 (see also fig. 6). Incision was made directly inward to the wall of the ventricle. The plane of excision was then sloped somewhat forward so that at the falx the removal was about as far anterior as the end of the ventricle. The line of removal as seen on the surface is indicated in fig. 7.

[1] Penfield, W., and Gage, L. "Cerebral Localization of Epileptic Manifestations." *Arch. Neurol. and Psychiat.*, **30**, 709, 1933.

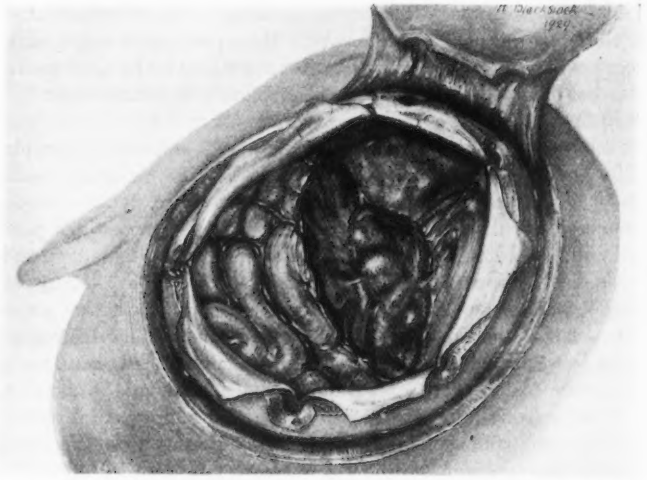

FIG. 6.—The artist's conception of the extent of the lobe amputation in Case 2.

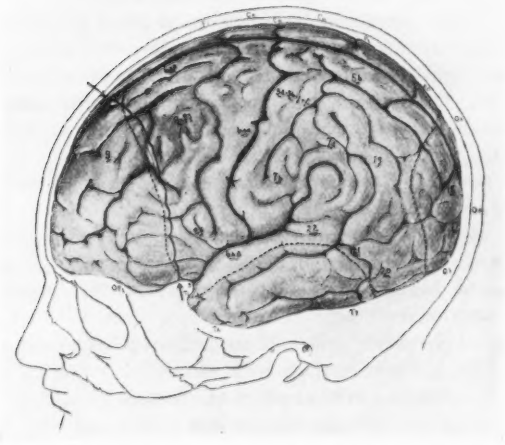

FIG. 7.—Surface projection of the amputation done in Case 2. The traction of the huge scar probably pulled the whole hemisphere forward so that the line of removal should be placed farther posterior.

During the operation, which was done under local analgesia, the patient was able to talk with us intelligently. Following it, at midnight, he was mentally clear but did not remember about the operation nor did he seem to recall recent events. In the first week after operation he became disorientated and somewhat confused mentally and developed a hemiparesis. He had difficulty in finding words.

One week after operation he had become well orientated for place and partially for time. Memory, however, was still deficient as far as recent events were concerned. The hemiparesis was improving. Two weeks after operation he was much clearer; he seemed slow but remembered recent and past events fairly well and could do simple arithmetical sums but not difficult ones, and the hemiparesis had disappeared.

Six months after operation the patient's physical examination showed him to be normal and he had returned to his former occupation. He reported that he was able to think better, act more quickly and that he was less irritable and quarrelsome than before operation. This should not be taken to mean that we consider frontal lobectomy would benefit a normal individual. The improvement over his former condition which continues up to the present time (five years later) is, of course, due to the complete arrest of his epileptiform seizures.

It is not wise to compare the man too closely with himself as he was before operation, because of the disappearance of the epilepsy. We can only study him objectively and in the light of the promise which he gave at the age of 16 before the accident.

Psychological examinations.—Dr. David Slight has examined the patient on several occasions and we here quote from his notes.

February 6, 1929 (two and a half months after operation): "General manner and appearance normal. When seen before leaving the Hospital the patient gave the impression of what can only be described as being 'blank' or 'out of touch.' Orientation good for time, place and person. On leaving Hospital he was distinctly hazy about time, but he has had no lapses in the past month.

"*Stream of thought*: Rate normal, flow coherent and logical. Denies any periods of confusion or dreaminess.

"*Emotional status*: Bright and consistently so. For a time after leaving the Hospital he was distinctly irritable, being upset over minor things, but he is now controlled and balanced. Denies any periods of depression or other fluctuations in emotional state.

"*Mental content*: No delusions, hallucinations or other abnormal phenomena. Memory is good, both for immediate and past events with the exception of a period of amnesia extending over much of the time in Hospital. For example, he can relate what he had for supper last night and also incidents at a theatrical show he attended a week ago. He can repeat six digits forward and five backwards. (One might claim that this is slightly below par since the average adult is expected to repeat six digits backwards, and the fourteen

year old level to repeat seven digits forward.) Intellect is good and he tests up to the fourteen year old level according to the Binet-Simon scale. Judgment and insight appear good.

"*Conduct*: No abnormalities so far as can be gathered. He apparently occupies himself in a normal fashion, reads the paper, goes out, and as already stated, attended a show last week. Writing and speech are normal.

"To sum up: It would appear that the patient shows no demonstrable mental change at the present time, and to judge from his previous occupation and other information it would seem that there is no mental loss. This is said with the reservation that any tests or judgments relate to what may be called a static condition, and do not entitle one to pass judgment on the patient in what may be called the dynamic situation."

Following a later examination (December 22nd, 1932, four years after operation) Dr. Slight again reported: "The patient was co-operative during the examination and gave a good account of himself. He is apparently free from any subjective sensations and has no complaints to make regarding his ability to live and behave in a normal way. Clinical examination of his mental state does not show any apparent indications of abnormality, and if one were not aware of the previous surgical procedures one would probably pass him without particular comment. On further questioning he does acknowledge one difficulty, and that is in regard to processes of mental arithmetic such as are involved in playing cards, and he particularly mentions a game called 'Five Hundred.' He is apparently unable to add figures together mentally and finds it necessary to use paper.

"Although his memory span tests up to the average adult level, a Binet-Simon examination made through the courtesy of Dr. W. T. B. Mitchell shows that on the Stanford revision of the Binet-Simon he has a mental age of 12 years and 4 months, with an intelligence quotient of 82. During this examination it was noted that he showed an apparent fatiguability and that there was a 'scatter' in the test. On the Healey completion test No. 2 he had a score of 73; 66 being regarded as the average level. The Healey completion 'B' test was completed in 45 seconds and 14 moves, which gives him a performance level of seventeen years.

"One point interesting and worthy of note is his spontaneous statement that emotionally he feels much more controlled now than in the past. He states that previously he was very antagonistic toward people and toward religious topics and such like, whereas now he finds himself more controlled in approaching and discussing such matters."

Vestibular reactions: Before operation the following examination was recorded in the Outpatient Clinic of the Department of Otolaryngology:

"February 7, 1928: Hearing losses of middle ear variety. Cold caloric test of both ears reveals normal response from each ear with 4 c.c. of ice-cold water. Both internal ears would seem to be normal but there is a hearing loss from the healed middle ear disease."

Six months after operation he was examined by Dr. W. J. McNally, who

made the following note (May 10, 1929): "Cold caloric test: Right ear: Four c.c. ice-cold water elicits a response of nystagmus from the horizontal canal—no response from the vertical canal, i.e. when head is erect; no dizziness. Ten c.c. of water at 120° F. elicits a few nystagmoid movements from the right horizontal canal. No response from the vertical canal, or very weak response.

"Left ear: Four c.c. ice-cold water—no response from either vertical or horizontal canal. Ten c.c. water at 120° F. elicits a definite nystagmus from the horizontal canal sharper than from the other ear; no response from the vertical canal. Ten c.c. of ice-cold water in the right and left ear produces a response from both the horizontal and vertical canals, but it is definitely diminished. This may be due to thickening of the drums from previous middle ear disease. There is no dizziness from any irrigation.

"Impression: Suggestion of diminished irritability of both internal ears, more marked in the vertical canals. There is a weakly positive de Kleijn sign from the left cerebral hemisphere. There is a long history of previous middle ear disease which has interfered with hearing."

Four years after operation Dr. McNally made a second note (December 7, 1932): "The right ear drum is thickened, milky white, intact. The left drum is thickened, milky white and shows scar in the postero-superior quadrant. No spontaneous eye nystagmus. While standing the patient is not disturbed by placing the head in any position nor is he disturbed or over-balanced by any sudden passive movement of the head or shoulders.

"Two and one half c.c. of ice-cold water in the left ear elicits a prompt nystagmus normal in character from the vertical and horizontal semicircular canals of that side. The duration of the nystagmus is quite short, about one minute. There is no dizziness. Two and one half c.c. of ice-cold water in right ear elicits the same normal response as above except that it is slightly less marked. In both cases the response from horizontal canals was more marked than from vertical canals. Ten c.c. at 120° F. in the right ear elicits prompt nystagmus from the horizontal and vertical canals, but definitely less marked when compared with the opposite side."

Dr. McNally summed up the vestibular examinations: "In other words there is no evidence that the quick phase of nystagmus shows any exaggeration toward the side of the lesion (de Kleijn's sign of a cerebral hemisphere lesion). If anything, this patient shows more response when the quick phase of nystagmus is to the opposite side of the lesion. When one considers the thickness of the drum one must conclude that both labyrinths are responding normally to stimulation.

"In the wheel chair with head erect (horizontal canals) normal response after ten turns to either side; no dizziness. It is worthy of note that after the caloric stimulation and rotation tests there was never at any time the slightest dizziness or past-pointing in spite of the fact that the other objective signs of labyrinthine stimulation were quite normal. I do not know quite what the significance of this fact may be."

Special sensory examination. November 28, 1932.

(*A*) *Spontaneous sensation.*—He has had no pain, numbness or tingling in the extremities, nor is there any lack of recognition of the position of the limbs. No paraesthesia of any nature.

(*B*) *Objective study.*

Light touch.—Recognition of cotton wool entirely normal, over the ulnar and radial sides of the forearms and over the lower limbs. Tactile acuity as tested with the von Frey hair is normal over the ulnar and radial borders of the arms, over the lower legs and also over the dorsi of the feet.

Pressure touch.—Not tested.

Localization.—Errors in centimetres. Ten trials.

Points tested on the right forearm and indicated by the left index finger	1·4	1·8	0·8	0·6	1·6	2·0	1·0	1·3	2·0	1·8	Average 1·4 cm.
Left forearm indicated by right index finger.	2·0	1·5	2·0	0·6	1·6	3·0	1·0	1·0	1·5	1·0	Average 1·5 cm.
Right leg indicated with right index finger.	2·0	0·5	0·8	2·8	1·5	0·5	2·5	1·5	3·2	4·0	Average 1·9 cm.
Left leg indicated with left forefinger.	0·7	2·7	0·3	1·0	2·0	1·5	1·7	0	0·3	0	Average 1·0 cm.

Roughness.—Not tested with the Graham Brown esthesiometer, but three grades of sandpaper were used, No. 2, No. $\frac{1}{2}$, and the reverse or smooth side of either of these called 0. Recognition of these various grades of sandpaper, interchanged, was quite normal over all the fingers, except for a slight confusion in the right fifth and also in the third left. There were no gross abnormalities in the skin, because of which there might be expected abnormal sensation. In any event these changes were very slight and may well not be significant.

Tickling and scraping.—Normal over the palms of both hands, over the soles of the feet. Cotton wool tickling and scraping were all normal.

Vibration.—Tested over the nails of the first and fifth fingers and the first and fifth toes and was quite normal.

Compass test.—Equally accurate on thenar and hypothenar regions of the two hands.

Pain.—(*a*) Superficial pain: Pinprick recognized normally over the lower arms and over the radial and ulnar borders of the hands, also over the lower legs and dorsi of the feet. (*b*) Pressure pain: This was tested in the forearms, in the upper third between the radius and ulna. Pain was recognized at 7 kgm. on the right side and at $7\frac{1}{2}$ kgm. on the left. In the legs the testing was done in the medial portion of the calf. On the right pain was recognized at 10 kgm. pressure; on the left at $8\frac{1}{2}$ kgm.

Temperature.—Differences of 27 and 34 degrees and 29 and 30 degrees were recognized over the lower extremities and over the forearms. A temperature difference of 29 and $29\frac{1}{2}$ degrees could not be differentiated.

Position.—Imitation of the position of one extremity by the other was prompt and accurate.

Passive movement.—Three to five degrees of movement were recognized in the fingers and in the toes accurately and without hesitation. No falling away of the unsupported upper limbs when the eyes were closed; lower extremities not tested.

Active movement.—(See above)

Weight.—Right hand supported able to differentiate between 100 and 105 grm. of weight and the left hand able to do the same. The right hand unsupported differentiated between 105 and 120 grm., 110 and 120 grm., and on one occasion between 100 and 105 grm., though on a second trial 100 to 105 grm. were called about the same. Left hand unsupported not able to differentiate between 100 and 105 grm., nor between 110 and 120 grm., but the difference between 105 and 120 grm. was recognized.

Size.—This was tested in the hands by the use of test tubes of the following diameters: 1·1, 1·6, 1·7 and 2 cm. The two middle tubes were confused rather readily but this was within normal limits.

Shape.—Triangle recognized in both hands promptly.

Form.—Calipers, two-point compass and throat sticks were all recognized readily.

Texture.—Cotton wool, paper and a rough towel all correctly named.

Consistency.—Hard rubber tip recognized as such. Thermometer bulb recognized as hard and cotton recognized as soft.

Figure writing.—

Left palm:—										
Written ..	..	7	4	3	2	1	6	8	9	0	5
Called ..	..	2	4	3	?	1	6	8	9	8	5
Also left palm:—										
Written ..	..	5	7	2	3	6	1	9	0	8	
Called ..	..	5	7	2	3	6	1	9	0	8	
Right palm:— (four trials)										
Written ..	..	5	7	2	3	6	1	9	0	8	
Called ..	..	5	7	2	3	5	5	5	0	8	
		5	7	2	3	6	5	9	9	8	
		5	7	2	3	8	1	9	0	8	
		2	7	2	3	6	1	9	8	8	

Summary of Findings on Sensory Examination.

(1) Suggestive error in spot finding on the right leg as indicated with the right index finger.

(2) Slight unexplained error in recognition of grades of sandpaper fifth finger right and third finger left.

(3) Left hand unsupported recognized the differences in weight less readily than the right.

(4) There seems to be definitely diminished acuity in recognition of figure writing in the right palm. This is irrespective of radial or ulnar border.

SUMMARY OF OBJECTIVE EXAMINATION.

The defects which we were able to detect in this case were as follows:—

(*a*) Small errors in sensory examination which are probably negligible, i.e., in spot-finding in right leg, in figure writing with the right hand and in weight differentiation with the left hand.

(*b*) Unexplained absence of dizziness and past-pointing after caloric and rotation stimulation although both labyrinths respond normally to stimulation. De Kleijn's sign of a cerebral hemisphere lesion was absent.

(*c*) Subjective decrease in capacity for mental arithmetic and bridge playing. Mental age of 12 years and 4 months with an intelligence quotient of 82 by Stanford revision of Binet-Simon test. Completion level of seventeen years in Healey completion test.

(*d*) Some lack of initiative. See discussion to follow.

FIG. 8.—Surface projection of the removal carried out in Case 3. There was much traction here also as in Case 2.

Case 3.—G. G., R.V.H. Right frontal lobectomy. Post-traumatic epilepsy, cerebral cicatrix.

This boy of 19 years received a severe head injury at the age of 8 and was referred by Dr. Colin Russel. Epileptiform seizures of right frontal lobe type had been present for one year. In November, 1931, a right frontal osteoplastic craniotomy was performed. Three cysts were found in the frontal pole and radical excision was carried out as indicated in fig. 8, cutting across the anterior end of the ventricle. The excised tissue, after evacuation of the cysts, weighed 34 grm.

There was a post-operative hæmorrhage which necessitated re-operation on the second day. Otherwise the recovery was uneventful, neurological

examination was negative on discharge and he has had no recurrence of the epileptic seizures up to the present, three years later.

One year after operation, in December, 1932, he was examined with the following results:—

(1) Special sensory tests similar to those in Case 2 above were entirely negative.

(2) Audiographic and vestibular tests by Dr. Scott-Moncrieff were entirely normal.

(3) Psychometric examinations by Dr. David Slight may be summarized as follows:—

"He shows no apparent psychiatric difficulty. He appears to have adjusted well to work and has on several occasions been able to give public demonstrations of his firm's products in a large store.

"Since being at home he has continued to play such games as cards and tennis, and he has actually continued playing with a basketball team. It is said that there is no loss of ability in these games. In so far as reading, writing and arithmetic processes are concerned there is no apparent loss of function. His memory span is 8 digits forward and 6 backward. He appears to be interested in his work and has ambitions to make progress, hoping and planning to take up studies to further his work."

In summary the excision in this case was smaller than in the two former cases. The portion of brain removed was doubtless partially incapacitated before removal. Physical and psychological examinations reveal no defects.

Discussion.

It may be urged that to destroy a delicate instrument is not the best way of studying its function. But we have recorded in some detail the results of three frontal removals selected from many other available cases because of their suitability for study. It is always difficult to assess the value of the information from clinical cases as we are not carrying out experiments on normal patients, but, rather, desperate operations upon patients in the brain of each of whom there was abnormality to begin with. With these criticisms in mind the cases presented still seem to offer an opportunity of making deductions of value with regard to the frontal lobe, deductions both positive and negative.

It is evident that removal of large portions of the brain may be carried out without even temporary loss of consciousness. The vestibular reactions were normal in the two cases carefully examined. But in the large left frontal removal (Case 2) there was unexplained absence of dizziness and past-pointing after caloric and rotary stimulation. This defect was not present in the smaller removal (Case 3) and was not tested for in Case 1.

The removal of left frontal lobe in Case 2 had been carried out in

this case back to within one or two centimetres anterior to the precentral gyrus. In its lower extent the line of removal crossed Broca's convolution not far from the anterior end of the fissure of Sylvius. At the base of the hemisphere the removal skirted closely the posterior edge of the orbital plate and lesser wing of the sphenoid. Mesially the plane of removal was more anterior than laterally.

Aphasia in this man did not develop immediately and disappeared within three weeks, leaving behind no difficulty in speech whatever. The disturbance of speech was therefore attributable to transient neighbourhood change in cerebral structures which had not been removed. Special psychological tests record a normal level for a man of his limited education. He showed at no time reflex forced grasping.

What defects has he? He, himself, is conscious of only one unfavourable sequel to operation, that is difficulty in performing mental arithmetic and in playing bridge (a game which calls, no doubt, for a certain limited type of memorization and computation!). If he can write the figures down and see them he says he can do his arithmetic. But even after five years he cannot summon the figures and add or subtract them in his head as easily as formerly. That ability seems to have been partially removed with the amputation.

Is there anything else lacking in this man, perhaps lacking since the original laceration of his frontal lobe? His mother praises him as being docile at home, but admits that he may have shown too little initiative ever since his injury. His father is head groundsman for McGill University, the son having worked under him for two years before operation and for more than a year afterwards, was laid off only along with others at the time of a general "cut." The father states that as a workman he never had a better helper, "but," he added, "he never had a job that I didn't get for him." He should have added "since the accident," for it may be recalled that this patient had had enough initiative at the age of 16 to find his way to England, and had secured himself a job there.

To sum up: this patient is a likeable fellow, a good workman and a useful citizen. It is quite certain he will never be a revolutionist. He has lost something that psychometric examination does not evaluate. He has lost initiative; not all of it, but much of it.

The extirpation of the right frontal lobe in Case 1 was the largest of the three removals, and may be discussed at greater length. To recall the details, this was the case of a woman of 43 whose lobe contained a calcified oligodendroglioma and whose amputation was carried back to

within a centimetre of the motor gyrus all the way down to the lowest frontal gyrus. From this line it passed across cleanly to the mid-line so that the septum pellucidum and the anterior two or three centimetres of the sectioned corpus callosum were visible after the removal (fig. 1).

To judge what this patient had lost by being deprived of nearly all of her right frontal lobe demands that an estimate be made of what she would have been had she had a normal right frontal lobe at that age. Because one of us (W. P.) had known her intimately from childhood we believe it is possible to evaluate the mental and personal changes. This we have undertaken at all events.

The history was long. For twenty-three years before operation there were Jacksonian seizures at very long intervals, which indicates that the oligodendroglioma was probably present for that length of time, an increase in the rate of growth doubtless occurring towards the end. The removal was of lobe and tumour, not of tumour alone. This was borne out by the post-mortem examination, which also showed that other areas of the brain were normal.

The rapid recovery and relief from the symptoms of compression do not concern us. The fact of the compression renders a comparison of her state immediately before operation with that afterward of no value. Such comparison would, of course, show only improvement. The analysis must go back to a much earlier period.

After operation she resumed her duties as wife and the mother of six children with greatly increased efficiency. But she was conscious of not being quite as alert mentally as she should be. This is best expressed in her own words. In July, 1929, seven months after operation, she wrote :—

> " Dr. Taylor asked me if I felt that mental activity was improving, and I said ' Yes,' but it seems as though each time I feel encouraged that way I do a series of very stupid things. Perhaps it is just a case of ' pride goeth before a fall ' and is the time one needs to be wary. I am trying to be more alert, sometimes it seems to be very slow progress, but still it is progress I am sure. If you have any advice to offer as to how to learn to think, how to get something of an education when old, &c., it will be gratefully received."

Her greatest difficulty was in household administration and she did not discipline the younger children as she had done when she herself was younger, although her general health was excellent. Nevertheless, she was still careful of her own person and orderly. Her sense of humour, memory, and insight into the thought and feelings of others was altogether unimpaired. She was capable of intelligent conversation and did not

talk either more or less than good taste demanded. Another letter from California may be quoted, written this time on the first aniversary of her operation :—

"It has been a very wonderful year with new life, new strength, new hope . . . I need firmly to convince myself that I am not really slow, nor stupid, not incapable, &c., and the rest will come.

"We will often think of you at Christmas and I am thankful I can picture you as you will be—the sunshine in the dining room and study, the cheery open fire, and the children going out to skate and coast or ski, the cars slipping and sliding, the cold crunch of the snow."

This shows insight, vivid memory and power of expression. In her home there was little or no discord. Her husband was patient and sympathetic and her children reflected the unselfish personality of their mother. Her own home provided in some ways a better background for study than the consulting room of the psychologist. The following test, though not sanctioned by psychological usage, may illustrate her shortcomings.

One day about fifteen months after operation she had planned to get a simple supper for one guest (W. P.) and four members of her own family. She looked forward to it with pleasure and had the whole day for preparation. This was a thing she could have done with ease ten years before. When the appointed hour arrived she was in the kitchen, the food was all there, one or two things were on the stove, but the salad was not ready, the meat had not been started and she was distressed and confused by her long continued effort alone. It seemed evident that she would never be able to get everything ready at once. With help the task of preparation was quickly completed and the occasion went off successfully with the patient talking and laughing in an altogether normal way.

Although physical examination was negative and there was no change in personality or capacity for insight, nevertheless the loss of the right frontal lobe had resulted in an important defect. The defect produced was a lack of capacity for planned administration. Perhaps the element which made such administration almost impossible was the loss of power of initiative. If we express it as she did with no attempt at analysis: she could not "think well enough," was a little "slow," a little "incapable."

In Case 3 the removal of the frontal pole, about half of the lobe, produced no detectable loss of function. This may be due to the fact that we could not study this boy before his accident. Or it may be due

to the fact that the anterior one half of the frontal lobe subserves only transferable function.

Conclusions.

Large amputations of the frontal lobe, if the precentral gyrus be left intact, produce surprisingly little disturbance of function which can be detected by ordinary methods of examination. There is no disturbance of the control of micturition, no forced grasping, no alteration of tone of the extremities or in the activity of deep or superficial reflexes.

In Case 2 the operative removal affected only the middle one-third of the left frontal lobe, as the anterior one-third had already been destroyed by the traumatic injury, if one may arbitrarily so divide the lobe. This removal of the middle one-third in a right-handed man produced a partial loss of his capacity for mental arithmetic (oral as distinguished from written). The patient also had an unexplained absence of dizziness and past-pointing after rotation and caloric tests, even though vestibular function was otherwise normal.

Detailed studies of sensation showed only changes that we presume to be within the limits of normal spontaneous variation. In Case 2 there was decreased appreciation of figures written upon the palm of the contralateral hand which may perhaps be related to the difficulty that the patient noted in the visualization of figures in "mental arithmetic."

The removal of approximately the anterior half or two-fifths of the right frontal lobe in Case 3 was not associated with any alteration, neurological or psychological, that we can detect.

The two larger removals (Cases 1 and 2), present certain important defects in common and we consider these removals to have begun at the time of the origin of the initial lesion and merely to have become complete at the time of operation. Neurologically each was normal. By the ordinary psychometric tests each would have to be judged normal although neither would rank very high. Each patient was lacking in initiative. Each was very good-natured and co-operative which may in some cases perhaps be an evidence of lack of initiation of ideas. Although it may not be of value here we may also remark in passing that we have in several other cases been told by relatives that removals of a very large area of frontal lobe with included neoplasm have resulted in marked improvement in the patient's temper.

Insight and capacity for introspection were preserved. Capacity to follow instruction was unimpaired, but initiative and capacity for

planned action were clearly defective. This was especially true of the woman of 43. She had become incapable of discerning for herself possible courses of action so that she might choose. If others presented to her the possibilities she made up her mind quite easily, and when a task lay before her there was no reluctance nor hesitation in undertaking it.

In so far as final conclusions from the first two cases are justifiable, it may be stated that maximum amputation of right or left frontal lobe has for its most important detectable sequel impairment of those mental processes which are prerequisite to planned initiative.

Notices of Recent Publications.

Intercortical Systems of the Human Cerebrum. By Joshua Rosett. Milford: Columbia University Press, 1933. Pp. 135, with 41 illustrations. Price 15s.

The ingenious method of splitting the white matter of the brain into its natural layers devised by the author has been applied by him with painstaking skill to the study of the intercortical pathways of the human cerebrum. Briefly the method consists in "exploding" the brain by saturating it with CO_2 under pressure and suddenly releasing the pressure. The layers of cleavage are then carefully dissected out and studied in flat sections stained by the Weigert-Pal method. The value of this method for the study of the intercortical connections is well shown by the present monograph, although the author confesses that the cartography of these systems is by no means complete. But even in the short time that has elapsed since the method was perfected the main subcortical and deeper connections have been mapped out. Among the many interesting observations which the book brings to light, the shortness of the subsulcine U fibres, and the fact that they are interrupted by any annectant gyrus in their path is somewhat surprising. The author has also shown that the inferior longitudinal fasciculus consists of many shorter systems uniting neighbouring parts of the brain, and that few if any fibres pass in it from the occipital to the frontal pole.

In addition to providing a remarkably complete survey of the white fibres of the cerebrum, the author has been able to criticize the work of the older investigators in the light of the new facts which his technique has furnished. The monograph is thus not only a record of original observations, but a well-informed survey of the whole field of intercortical fibres systems.

L'Angiographie cérébrale. Par Egas Moniz. Paris: Masson et Cie, 1934. Pp. 327. Price 90 fr.

In this monograph Professor Moniz has given an account of his experiences with "thorotrast" since the autumn of 1931. This substance has been found to possess many advantages over sodium iodide which was used in his earlier work. It appears to be non-toxic and safe. But it is specially valuable because, as it mixes slowly with the blood, it can be followed into the intra-cerebral veins and venous sinuses. This property also enables it to be used

for injections of the vertebral artery, via the common carotid. It is thus possible to investigate every region of the brain for the presence of a tumour or aneurysm. By taking a series of plates at intervals of two or four seconds the rate of the blood-flow through any arterial system can be timed, and the presence of arterial stenosis or aneurysm may thus be diagnosed. The method has also been used in the diagnosis of congenital malformations in the Circle of Willis.

The technique of the injection is comparatively simple, but the interpretation of the plates would be difficult without an accurate knowledge of the normal appearances of the cerebral arteries and veins when viewed by this technique. A large part of the book is, therefore, taken up with a description of the normal and with the more common abnormalities. This description is greatly aided by the series of excellent plates. Altogether it is a valuable guide to a method of diagnosis which is now emerging from the experimental stage and being widely used.

Une Nouvelle Syphilis Nerveuse, ses formes cliniquement inapparentes. Par PAUL RAVAUT. Paris: Masson et Cie, 1934. Pp. 200. Price 45 fr.

In this monograph Ravaut sums up his experiences, over a period of more than thirty years, of the cerebrospinal fluid during the secondary and latent periods of syphilis. The evidence which he collects is impressive although not altogether concordant. On the whole he makes out a strong case for the assumption that clinical neurosyphilis is based in the vast majority of cases on an infection of the meninges of the nervous parenchyma during the late primary or secondary periods of the disease. The frequency of such infection, as shown by the statistics of many workers, varies from 51 to 86 per cent. in acquired, and from 25 to 100 per cent. in hereditary cases. The percentage of meningeal reactions appears to be greatest between six months and two years after infection, dropping rapidly towards the close of the third year. Which of these cases are destined to be included in the 15 per cent. of clinical neurosyphilis is a question which Ravaut has set himself to settle. The answer he gives is that those cases with "complete" reactions (i.e. not only excess of cells and protein, but also positive Wassermann and colloidal reactions) in which the fluid returns slowly and incompletely towards normality under treatment will probably develop neurosyphilis later. A similar prognosis may be made apart from the results of treatment when the cell count includes plasma cells and polymorphonuclears as well as lymphocytes. But it appears to be impossible to foresee what form the clinical disease will take. He is convinced that the solution of the problem of neurosyphilis lies in thorough treatment during the primary and secondary stages of the disease controlled by lumbar puncture, which should be performed at least at the end of the third year. The value of malaria in the prophylaxis of neurosyphilis which has been suggested by recent Viennese work is discussed towards the end of the book.

As a survey of the author's life-work this book is of value, although, in spite of its title, it contains little that has not already been published. It suffers from the lack of a comprehensive bibliography and of an index.

Speech Disorders: A Psychological Study of the Various Defects of Speech. By S. M. STINCHFIELD. London: Kegan Paul. 1933. Pp. 341. Price 15s.

The merit of the first part of this book, dealing with the nature of speech disorders, lies in the setting forth of divisions and of relevant bibliography rather than in its mode of presentation which is neither as critical nor as well-informed as one would wish. Evidently with enormous labour the writer has read all she could find concerning her subject, but where clinical experience and selection were necessary she has fallen short. The lengthy chapters on: "Pathological Conditions Affecting the Speech Function—Dysarthria Cerebropathica, Dysarthria Neuromusculopathica"; on "Dysphemia, or Backgrounds which Produce the Stutterer—Dysphonia or Voice Defects" and on "Dyslogia and Dysphasia" are bookish and artificial on this account. If one may judge from the lists of Greek neologising given in Part I, there is now among the psychologists who study this subject a rage for classifying and naming which is reminiscent of the older days of psychiatry. The second part of the book gives the statistical findings in some personal investigations. These were made by Dr. Stinchfield on 3,000 college women and some public school groups, and they covered personality, left or right-handedness and oral and silent readings in their relation to speech. Questionnaires and tests were used. The book is detailed but contains much undigested factual material.

Die Neurologie des 1—7 Jahrhunderts n. Christus. By Dr. WALTER CREUTZ. Leipzig: Georg Thieme. 1934. Pp. 106. Price M. 7.80.

As Dr. Creutz points out in his foreword, neurology has received little attention from the historians of medicine. This gap he has essayed to fill for the period that stretches roughly from the Augustan Age to the fall of the Empire of the west. Beginning with Celsus, he takes in turn Soranus and Coelius Aurelianus, Aretaeus, Oribasius, Aetios, Alexander of Tralleis and Paulus Aegineta, and translates into German the relevant passages in their writings. Galen he mentions only briefly here as Falk's comprehensive monograph is available, but in the suceeding section, in which he makes a comparative study of the knowledge and theories of the period, he devotes much space to this incomparable observer. The zenith of neurological study during the Roman Empire was in the first two or three ceuturies when there flourished not only Galen but the clinicians with Soranus at their head, and Aretaeus only a short

distance after him. This carefully written monograph is a valuable source-book for the many data of neurological interest which are scattered rather inaccessibly through the extant writings of an interesting, if remote, age of medicine.

Lateral Dominance and Visual Fusion. By C. A. SELZER. Harvard Monographs in Education. No. 12. Cambridge: Harvard University Press. 1933. Pp. 119. Price 6s.

This monograph deals with the relation of heterophoria and alternating vision to the disabilities in reading, writing, spelling and speech generally, which are such a handicap educationally to some children. The alleged importance of lateral dominance, especially as seen in hand and eye, is examined, and the author puts forward with indignant zeal his conviction that treatment of mirror-reading and related troubles should be by the wearing of prisms; oculists are on the whole understandably dubious about his claims. The discussion of tests for lateral dominance is an interesting part of the monograph.

L'Enfant et le Langage. Par HENRI DELACROIX. Paris: Librairie Félix Alcan. 1934. Pp. 118. Price 12 fr.

M. Delacroix here carries further some of the questions raised in his well-known larger work on language and thought. Many studies on the development of speech in children have appeared in the last few years, and here they are examined critically. The superficial formulations which sometimes pass muster in psychology are exposed, and the valuable findings of Stern, Yerkes, Kellogg, Bühler and others are reviewed. Although brief the book leaves few aspects of the subject untouched, and the style is, as always with the author, felicitous.

Konstitution und Prozess in der Schizophrenie. von Dr. Skalweit. Leipzig: G. Thieme. 1934. Price M. 4.50.

The author has applied the Rorschach method to the study of schizophrenia especially "Prozess-Schizophrenie." The problem which particularly occupied his attention is not, however, so prominent in English psychiatry, where the conception of a schizophrenia determined by progressive structural changes has not had general recognition.

From the results of his investigation he concludes that a schizophrenic psychosis does not consist in a purely quantitative intensification of the specific schizoid type of reaction but in a qualitative change in this. He draws unduly wide inferences from a test that is still on probation. The typological doctrines of Kritschmer are also examined, and the author shows his interest in some national pre-occupations by a discussion of the relationship between the schizothyme type and the Nordic race.

Investigation into the Causes of Mental Deficiency. By H. O. WILDENSKOV. Copenhagen: Levin and Muskgaard. London: Humphrey Milford. 1934. Pp. 113.

The author of this work, who is the medical superintendent of a Danish institution for mental defectives, has carried out a careful and painstaking research into the differences in family incidence of deficiency between two groups of his patients, the one group being composed of fifty mild cases and the other of fifty severe ones. Various additional aspects of the two groups were also investigated, but the family studies supplied the most important data on ætiology. With a refreshing lack of mathematical ostentation Dr. Wildenskov presents his material and points out how much fewer were the definitely exogenous cases that is often asserted to be the common proportion. He emphasizes that the discovery of neurological abnormalities does not necessarily indicate pre-natal or post-natal trauma, since inheritable structural anomalies or predispositions may be in question. In view of the relatively small numbers he is cautious in his conclusions, but he finds strong evidence of the hereditary factor being more significant in the mild than in the severe cases.

Mental Health: Past, Present and Future. By A. H. Ruggles. Baltimore: The Williams and Wilkins Company. 1934. Pp. 104.

These attractively composed lectures have a welcome honesty and lucidity. There are three of them: The first is historical, while the second deals with the present situation in psychiatry, especially in its American developments. The last lecture, which looks to the future, is soberly optimistic about mental health. The author puts his hope in better training of physicians and other leaders, as well as in better training of the public, who must not only be led but co-operate, so that the social and individual problems which weigh so heavily now may be lightened if not solved.

Die Irrtümer der Psycho-analyse. By HENRIK EGYEDI. Vienna and Leipzig: Wilhelm Braumüller. 1933. Pp. 86. Price Rm. 2.80.

While the majority of observers are now content to show distrustful politeness, or at least reserve, towards psycho-analysis, there are some who are goaded into critical or irritable examination of its claims. These provocative claims are more or less proof against such onslaughts, because it is not to the court of logic or scientific method that psycho-analysis appeals. The objections made here by Dr. Egyedi are in the main valid if applied to any scientific procedure where the necessity for repeating and verifying observations, testing hypotheses, and predicting outcomes in given circumstances can be taken for granted. But psycho-analysis is not a procedure of this kind;

statistical and other controls have played practically no part in it. Some of his strictures are less applicable to the strict doctrine of Freud himself than to the still more speculative form that has developed in this country in the last few years. On the other hand, it is no longer possible to accuse the Freudians, as the author does, of a slavish devotion to their master; the devotion of psycho-analysts is now becoming, like so much else, national or local, and London looks backwards and sideways, not upwards, upon Vienna. It is doubtful, whether, such methodological examination as this will have much more effect than had the similar criticisms of phrenology or homœopathy. Psycho-analysts are by temperament and training unlikely to be influenced by attacks on such lines, even when mitigated by admiration for Freud; others will prefer to wait until the hypotheses of psycho-analysis can be satisfactorily tested.

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EDITOR.